AM

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 598 359 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
14.06.2000 Bulletin 2000/24

(51) Int. Cl.[7]: **A61K 31/70**, C07H 15/203

(21) Application number: **93118365.1**

(22) Date of filing: **12.11.1993**

(54) Hypoglycemic dihydrochalcone derivatives

Hypoglykämische Dihydrochalconderivate

Derivés de dihydrochalcone hypoglycémiques

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **12.11.1992 JP 30148592**
18.02.1993 JP 2877093
25.02.1993 JP 3598893

(43) Date of publication of application:
25.05.1994 Bulletin 1994/21

(73) Proprietor:
TANABE SEIYAKU CO., LTD.
Chuo-ku Osaka (JP)

(72) Inventors:
- **Tsujihara, Kenji**
Saitama-ken (JP)
- **Hongu, Mitsuya,**
Tanabe Seiyaku Omiya-ryo
Saitama-ken (JP)
- **Funami, Nobuyuki,**
Toho-mansion
Tokyo-to (JP)
- **Inamasu, Masanori**
Saitama-ken (JP)
- **Arakawa, Kenji**
Saitama-ken (JP)

(74) Representative:
Hansen, Bernd, Dr. Dipl.-Chem. et al
Hoffmann Eitle,
Patent- und Rechtsanwälte,
Arabellastrasse 4
81925 München (DE)

(56) References cited:
EP-A- 0 172 721

- **J. CLIN. INVEST. vol. 79 , 1987 pages 1510 - 1515 L. ROSETTI ET AL 'Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats.'**
- **BIOCHIM. BIOPHYS. ACTA vol. 71 , 1963 pages 688 - 700 D.F. DIEDRICH 'The comparative effects of some phlorizin analogs on the renal reabsorption of glucose.'**
- **ARCH. BIOCHEM. BIOPHYS. vol. 117, no. 2 , 1966 pages 248 - 256 D.F. DIEDRICH 'Competitive inhibition of intestinal glucose transport by phlorizin analogs'**
- **AMER. J. PHYSIOL. vol. 224, no. 3 , 1973 pages 552 - 557 H. VICK ET AL. 'Reevaluation of renal tubular glucose transport inhibition by phlorizin analogs.'**
- **ACTA ALIMENT. vol. 11, no. 1 , 1982 pages 31 - 37 P. SZAB ET AL 'Effect of a synthetic dihydrochalcone sweetener (chinoin-401) on carbohydrate metabolism.'**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

Printed by Xerox (UK) Business Services
2.16.7 (HRS)/3.6

Description

[0001] The present invention relates to hypoglycemic agent comprising as an active ingredient a dihydrochalcone derivative or a pharmaceutically acceptable salt thereof.

Prior Art

[0002] Although diet therapy is essential in the treatment of diabetes, when diet therapy does not sufficiently control the conditions of patients, insulin or oral antidiabetic is additionally used. There have been used as an antidiabetic biguanide compounds and sulfonyl urea compounds, however, these antidiabetics have various side effects, for example, biguanide compounds cause lactic acidosis, and sulfonyl urea compounds cause significant hypoglycemia. Under such circumstances, it has been desired to develop novel drugs for treatment of diabetes having no side effects.

[0003] Recently, it has been reported that hyperglycemia participates in the outbreak and deterioration of diabetes, i.e. glucose toxicity theory. That is, chronic hyperglycemia leads to progressive impairment in insulin secretion and contributes to insulin resistance, and as a result, the blood glucose concentration is increased so that diabetes evaluates [cf. Diabetologia Vol. 28, p. 119(1985), Diabetes Care, 13, 610 (1990), etc.].

[0004] This theory is proved as follows. That is, when the blood glucose concentration in diabetic animals is controlled at normal for a long time without using insulin, the conditions of diabetic animals are ameliorated to be normal [cf. Journal of Clinical Investigation, Vol. 79, p. 1510 (1987), Vol. 80, p. 1037 (1987), Vol. 87, p. 561 (1991), etc.]. In these investigations, phlorizin was used by subcutaneous administration as a drug to normalize the blood glucose concentration.

[0005] Phlorizin is a glycoside which exists in barks and stems of Rosaceae (e.g. apple, pear, etc.), and was discovered in the 19th century, and has been studied since. Recently, it has been found that phlorizin is an inhibitor of Na^+-glucose co-transporter which exists only at chorionic membrane of the intestine and the kidney, and that phlorizin inhibits the renal tubular glucose reabsorption and promotes the excretion of glucose so that the blood glucose is controlled.

[0006] However, when phlorizin is administered orally, most of it is hydrolyzed into phloretin, which is the aglycon of phlorizin, and glucose, and hence, the amount of phlorizin to be absorbed is so little that the urine glucose excretion effect of phlorizin is very weak. Besides, phloretin, which is the aglycon of phlorizin, has been known to inhibit strongly facilitated diffusion-type glucose transport carrier, for example, when phloretin is intravenously administered to rats, the brain glucose is attenuated [cf. Stroke, Vol. 14, 388 (1983)]. However, when phlorizin is administered for a long time, there may be bad effects on various tissues, and hence, phlorizin has not been used as an antidiabetic.

[0007] Besides, 2'-O-(β-D-glucopyranosyl)-6'-hydroxydihydrochalcone, 2' - O-(β-D-glucopyranosyl)-4,6'-dihydroxydihydrochalcone and 2'-O-(β-D-gluco - pyranosyl)-6'-hydroxy-4-methoxydihydrochalcone have been known to inhibit photophosphorylation at chloroplast [cf. Biochemistry, Vol. 8, p. 2067 (1967)]. Moreover, 2'-O-(β-D-glucopyranosyl)-4,6'-dihydroxydihydrochalcone has also been known to inhibit Na^+-glucose co-transporter at the kidney [cf. Biochim. Biophys. Acta, Vol. 71, p. 688 (1963)]. However, it has never been disclosed that these compounds have urine glucose increasing activity even by oral administration.

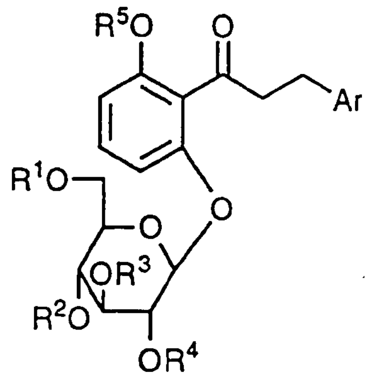
[0008] The nature of the inhibition of intestinal glucose transport in vitro by phlorizin, 4'-deoxyphlorizin and 4-metoxyphlorizin was studied in Arch.Biochem.Biophys., 117 (1966) p. 248-256 and Amer.J.Physiol., 224 (1973) p. 552-557. EP-A-172 721 discloses the use of phlorizin, its gluconuride and 4-deoxyphloretin-2-D-glucoside in the treatment of cancer.

Brief Description of the Invention

[0009] An object of the present invention is to provide dihydrochalcone derivatives which inhibit the renal tubular glucose reabsorption and/or inhibit the absorption of glucose at the intestine, and show excellent hypoglycemic activity as well as an aglycon thereof has weak inhibitory activity of facilitated diffusion-type glucose transport carrier. Another object of the present invention is to provide a hypoglycemic agent comprising as an active ingredient a dihydrochalcone derivative of the present invention or a pharmaceutically acceptable salt thereof.

Detailed Description of the Invention

[0010] The present invention relates to the use of a dihydrochalcone derivative of the formula [I]:



[I]

wherein Ar is 1) a phenyl group optionally substituted by 1 to 2 groups selected from a C_{1-6} alkyl group; a trihalogeno-C_{1-6} alkyl group; a C_{1-6} alkoxy group optionally substituted by a C_{1-6} alkoxy group; a (C_{1-6} alkoxy)-carbonyloxy group optionally substituted by a C_{1-6} alkoxy group; a dialkylamino group; a C_{2-7} alkanoyloxy group optionally substituted by a C_{1-6} alkoxy group, a (C_{1-6} alkoxy)-carbonyl group or an amino group; a halogen atom; a hydroxy group; a C_{1-6} alkylthio group; a phenoxycarbonyloxy group; a C_{1-6} alkylenedioxy group; and a benzoyloxy group optionally substituted by a C_{1-6} alkoxy group; 2) a fury group; 3) a thienyl group; or 4) a naphthyl group, R^1 is a hydrogen atom; a C_{2-7} alkanoyl group optionally substituted by a C_{1-6} alkoxy group; a (C_{1-6} alkoxy)-carbonyl group; or a benzoyl group, R^2 is a hydrogen atom; a C_{2-7} alkanoyl group optionally substituted by a C_{1-6} alkoxy group; a (C_{1-6} alkoxy)-carbonyl group; or a α-D-glucopyranosyl group, R^3 and R^4 are each a hydrogen atom; a C_{2-7} alkanoyl group optionally substituted by a group selected from a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, and an amino group; a (C_{1-6} alkoxy)-carbonyl group optionally substituted by a C_{1-6} alkoxy group; a benzoyl group; or a phenoxycarbonyl group, and the group of the formula OR^5 is a protected or unprotected hydroxy group or a C_{1-6} alkoxy group, provided that when R^1, R^2, R^3 and R^4 are hydrogen atoms and OR^5 is a hydroxy group, Ar is different from a 4-hydroxyphenyl group, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for preventive or therapeutic application to diabetes.

[0011] The dihydrochalcone derivatives [I], the active ingredient of the present invention, show excellent hypoglycemic activity based on the urine glucose increasing activity thereof. For example, when the active ingredient [I] of the present invention is administered to rats, the amount of glucose to be excreted into urine for 24 hours is about 5 to 40 times as much as those when phlorizin is administered. In addition, when the active ingredient [I] of the present invention is orally administered to glucose-loading diabetic mice, the increment in the blood glucose concentration thereof is remarkably attenuated. Thus, the hypoglycemic agent of the present invention is useful in the prophylaxis or treatment of diabetes. The urine glucose increasing activity of the active ingredient [I] of the present invention is postulated to be based on the inhibitory activity of the renal glucose reabsorption, which is different from the conventional hypoglycemic agents.

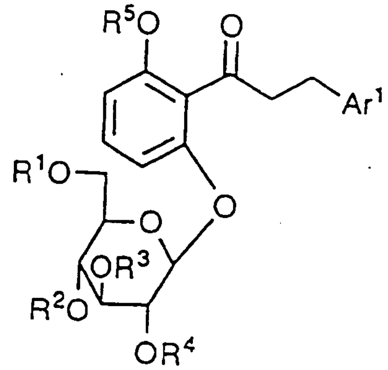
[0012] Besides, the active ingredient of the present invention is low toxic, for example, when 2'-O-(β-D-glucopyranosyl)-6'-hydroxy-4-methoxydihydrochalcone or 2'-O-(2,3-di-O-ethoxyacetyl-β-D-glucopyranosyl)-6'-hydroxy-4-methoxydihydrochalcone was orally and continuously administered to rats at a dose of 1000 mg/kg for 28 days, no rat was dead.

[0013] The aglycone, which is a hydrolysate of the active ingredient of the present invention, is characteristic in its extremely weak glucose-uptake inhibitory activity, which is different from phloretin. For example, human erythrocyte was incubated with D-[3-^{3}H]glucose for one minute, and the radioactivity of erythrocyte was measured in order to estimate the amount of glucose to be incorporated into erythrocyte. In this experiment, when an aglycon of the active ingredient [I] of the present invention, 2',4,6'-trihydroxdihydrochalcone, or 2',6'-dihydroxy-4-methoxydihydrochalcone was added to the reaction system, the amount of glucose to be incorporated into erythrocyte is 92.7 %, and 91.0 %, respectively as compared with the amount of glucose to be incorporated into erythrocyte when no test compound was added. On the other hand, the amount of glucose to be incorporated into erythrocyte was 13.7 % when phloretin was added. Accordingly, the inhibitory activity of glucose incorporation into human erythrocyte of the aglycon of the active ingredient of the present is much smaller than that of phloretin, the aglycon of phlorizin, and hence, even though the active ingredient [I] of the present invention is partially hydrolyzed, the glucose concentration in tissues does not easily decrease.

[0014] In the present specification, a lower alkyl lower alkoxy etc. group means an alkyl, alkoxy etc. group having 1 to 8, preferably 1 to 6, most preferably 1 to 4 carbon atoms.

[0015] When a group of the formula: OR^5 is a protected hydroxy group in the active compounds [I], the protecting group may be ones which can be a protecting group for phenolic hydroxy group, for example, an acyl group such as a lower alkanoyl group optionally substituted by a group selected from a lower alkoxy group, a lower alkoxycarbonyl group, phenyl group and amino group; a lower alkoxycarbonyl group; a lower alkoxy-lower alkoxycarbonyl group; phenoxycarbonyl group; benzoyl group; or a lower alkoxybenzoyl group.

[0016] Among the active dihydrochalcone derivatives of the present invention, a compound of the formula [I-A]:



[I-A]

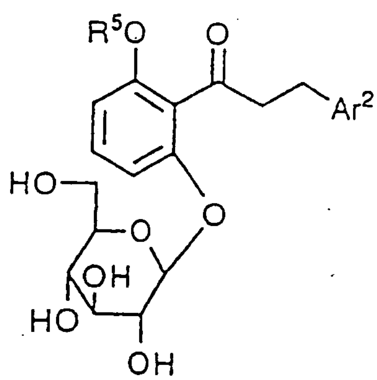
wherein R^1, R^2, R^3, R^4 and OR^5 are the same as defined above and Ar' is Ar as defined above provided that when R^1, R^2, R^3 and R^4 are hydrogen atoms and OR^5 is a hydroxy group, Ar^1 is different from a 4-hydroxyphenyl group, 4-methoxyphenyl group and phenyl group, or a pharmaceutically acceptable salt thereof, is a novel compound.

[0017] The pharmaceutically preferable compounds [I] are compounds of the formula [I] wherein Ar is phenyl group, a lower alkyl-substituted phenyl group, a lower alkoxy-substituted phenyl group, a lower alkoxycarbonyloxy-substituted phenyl group or a halogenophenyl group, the group of the formula: OR^5 is a protected or unprotected hydroxy group, and R^1, R^2, R^3 and R4 are all hydrogen atom, or compounds of the formula [I] wherein Ar is a phenyl group optionally having a substituent selected from a halogen atom, hydroxy group, a lower alkyl group, a lower alkoxy group, a lower alkanoyloxy group and a lower alkoxycarbonyloxy group, the group of the formula: OR^5 is a protected or unprotected hydroxy group, R^1 and R^2 are both hydrogen atom, and R^3 and R^4 are each a lower alkanoyl group optionally having a substituent selected from a lower alkoxy group, a lower alkoxy-lower alkoxy group, and amino group, a lower alkoxycarbonyl group, benzoyl group, or phenoxycarbonyl group.

[0018] The pharmaceutically more preferable compounds are compounds of the formula [I] wherein Ar is a phenyl group optionally having a substituent selected from a lower alkyl group and a lower alkoxy group, the group of the formula: OR^5 is hydroxy group or a hydroxy group protected by a lower alkanoyl group, R^1 and R^2 are both hydrogen atom, R^3 and R^4 are each a lower alkanoyl group, a lower alkoxy-substituted lower alkanoyl group, a lower alkoxycarbonyl group or a phenoxycarbonyl group, and especially the compounds of the formula [I] wherein Ar is a lower alkoxy-substituted phenyl group, and R^3 and R^4 are each a lower alkoxy-substituted lower alkanoyl group are preferable.

[0019] Moreover, other preferable compounds are novel compounds of the formula [I-A].

[0020] Among the novel compounds [I-A], preferable compounds are compounds of the formula [I-a]:

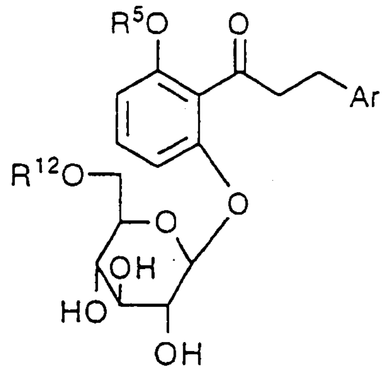


[I-a]

wherein Ar^2 is 1) a phenyl group substituted by 1 to 2 groups selected from a C_{1-6} alkyl group; a trihalogeno-C_{1-6} alkyl group; a C_{1-6} alkoxy group (other than 4-methoxy group) optionally substituted by a C_{1-6} alkoxy group; a (C_{1-6} alkoxy)-carbonyloxy group optionally substituted by a C_{1-6} alkoxy group; a dialkylamino group; a C_{2-7} alkanoyloxy group optionally substituted by a C_{1-6} alkoxy group, a (C_{1-6} alkoxy)-carbonyl group or an amino group; a halogen atom; a hydroxy group other than 4- hydroxy group; a C_{1-6} alkylthio group; a phenoxycarbonyloxy group; a C_{1-6} alkylenedioxy group; and a benzoyloxy group optionally substituted by a C_{1-6} alkoxy group; 2) a furyl group; 3) a thienyl group; or 4) a naphthyl group, and the group of the formula OR^5 is a protected or unprotected hydroxy group or a C_{1-6} alkoxy group, or a pharmaceutically acceptable salt thereof.

[0021] More preferable compounds are

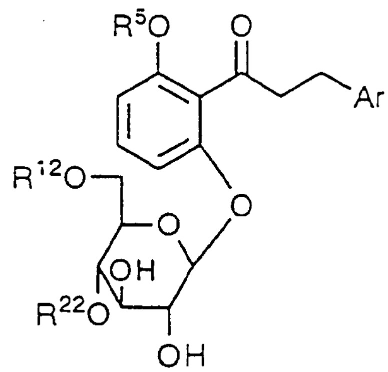
(1) compounds of the formula [I-c]:



[I-c]

wherein Ar and OR^5 are the same defined above; and R^{12} is a C_{2-7} alkanoyl group optionally substituted by a C_{1-6} alkoxy group; a (C_{1-6} alkoxy)-carbonyl group; or a benzoyl group.

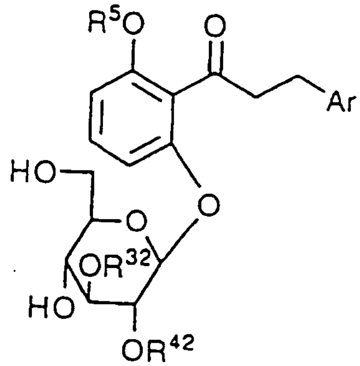
(2) compounds of the formula [I-d]:;



[I-d]

wherein Ar, R^{12} and OR^5 are the same as defined above; and R^{22} is a C_{2-7} alkanoyl group optionally substituted by a C_{1-6} alkoxy group; or a (C_{1-6} alkoxy)-carbonyl group,

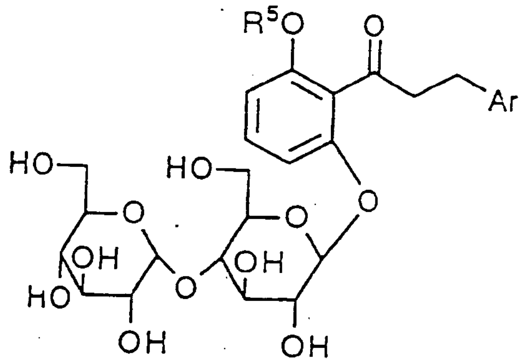
(3) compounds of the formula [I-e]:



[I-e]

wherein Ar and OR^5 are the same as defined above and R^{32} and R^{42} are each a C_{2-7} alkanoyl group optionally substituted by a group selected from a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, and an amino group; a (C_{1-6} alkoxy)-carbonyl group optionally substituted by a C_{1-6} alkoxy group; a benzoyl group; or a phenoxycarbonyl group,

(4) compounds of the formula [I-g]:



[I-g]

wherein Ar and OR^5 are the same as defined above,

[0022] Among the compounds [I-c], further preferable compounds are compounds of the formula [I-c] wherein Ar is a phenyl group optionally substituted by a group selected from a halogen atom, hydroxy group, a lower alkyl group, a lower alkoxy group, a lower alkanoyloxy group and a lower alkoxycarbonyloxy group, the group of the formula: OR^5 is a protected or unprotected hydroxy group or a lower alkoxy group, and R^{12} is a lower alkanoyl group optionally substituted by a lower alkoxy group; a lower alkoxycarbonyl group; or benzoyl group.

[0023] Among the compounds [I-d], further preferable compounds are compounds of the formula [I-d] wherein Ar is a phenyl group optionally substituted by a group selected from a halogen atom, hydroxy group, a lower alkyl group, a lower alkoxy group, a lower alkanoyloxy group and a lower alkoxycarbonyloxy group, the group of the formula: OR^5 is a protected or unprotected hydroxy group or a lower alkoxy group, and R^{12} and R^{22} are each a lower alkanoyl group optionally substituted by a lower alkoxy group; a lower alkoxycarbonyl group; or or benzoyl group.

[0024] Among the compounds [I-e], further preferable compounds are compounds of the formula [I-e] wherein Ar is a phenyl group optionally substituted by a group selected from a halogen atom, hydroxy group, a lower alkyl group, a lower alkoxy group, a lower alkanoyloxy group and a lower alkoxycarbonyloxy group, the group of the formula: OR^5 is a protected or unprotected hydroxy group or a lower alkoxy group, and R^{32} and R^{42} are each a lower alkanoyl group optionally substituted by a group selected from a lower alkoxy group, a lower alkoxy-lower alkoxy group, and an amino group; a lower alkoxycarbonyl group optionally substituted by a lower alkoxy group; or phenoxycarbonyl group.

[0025] Among the compounds [I-g], further preferable compounds are compounds of the formula [I-g] wherein Ar is phenyl group, a lower alkylphenyl group, a halogenophenyl group, hydroxyphenyl group or a lower alkoxyphenyl group, and the group of the formula: OR^5 is a protected or unprotected hydroxy group or a lower alkoxy group.

[0026] Among these compounds, the pharmaceutically preferable compounds are compounds of the formula [I-a] wherein Ar^2 is a C_{1-3} alkyl - phenyl group, a C_{2-3} alkoxy-phenyl group, a C_{1-6} alkoxy-carbonyloxy-phenyl group, or a halogenophenyl group, and the group of the formula: OR^5 is a protected or unprotected hydroxy group, or compounds of the formula [I-e] wherein Ar is a phenyl group optionally substituted by a group selected from a halogen atom, hydroxy group, a lower alkyl group, a lower alkoxy group, a lower alkanoyloxy group and a lower alkoxycarbonyloxy group, the group of the formula: OR^5 is a protected or unprotected hydroxy group, and R^{32} and R^{42} are each a lower alkanoyl group optionally substituted by a group selected from a lower alkoxy group, a lower alkoxy-lower alkoxy group, and amino group, a lower alkoxycarbonyl group, benzoyl group or phenoxycarbonyl group.

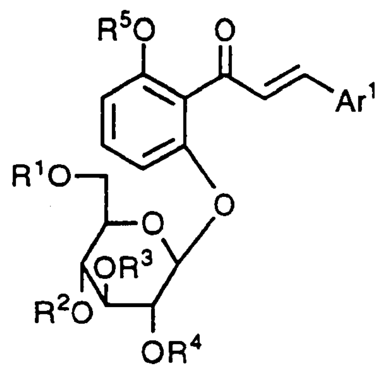
[0027] The pharmaceutically more preferable compounds are compounds of the formula [I-e] wherein Ar is a phenyl group optionally substituted by a group selected from a lower alkyl group and a lower alkoxy group, the group of the formula: OR^5 is hydroxy group or a hydroxy group protected by a lower alkanoyl group, and R^{32} and R^{42} are each a lower alkanoyl group, a lower alkoxy-substituted lower alkanoyl group, an amino-substituted lower alkanoyl group, a lower alkoxycarbonyl group or phenoxycarbonyl group, and especially the compounds of the formula [I-e] wherein Ar is a lower alkoxy-substituted phenyl group, and R^{32} and R^{42} are each a lower alkoxy-substituted lower alkanoyl group are preferable.

[0028] The active ingredient [I] of the present invention may be used in the form of a pharmaceutically acceptable salt thereof in clinical use. The pharmaceutically acceptable salt is salts with an inorganic acid (e.g. hydrochloric acid, sulfuric acid, etc.) or with an organic acid (e.g. acetic acid, methanesulfonic acid, etc.), or salts with an inorganic base (e.g. sodium, potassium, etc.) or with an organic base (e.g. ammonia, a lower alkylamine, etc.).

[0029] The active ingredients [I] of the present invention and pharmaceutically acceptable salts thereof may be administered either orally or parenterally, and or in the form of a pharmaceutical preparation in admixture with an excipient suitable for oral administration or parenteral administration. The pharmaceutical preparation is solid preparations such as tablets, capsules, powders, etc., or liquid preparations such as solutions, suspensions, emulsions, etc. When the active ingredient [I] is administered parenterally, an injection form is preferable.

[0030] The dosage of the active ingredient [I] of the present invention varies according to ages, weights and conditions of patients, or severity of diseases to be cured, but it is usually in the range of 1 to 100 mg/kg/day, preferably in the range of 5 to 40 mg/kg/day in case of oral administration. In case of parenteral administration, the dosage of the active ingredient [I] of the present invention is in the range of 0.1 to 50 mg/kg/day, preferably in the range of 0.5 to 10 mg/kg/day.

[0031] The compounds of the formula [I-A] may be prepared by subjecting a chalcone derivative of the formula [II]:



[II]

wherein Ar^1, R^1, R^2, R^3, R^4 and OR^5 are the same as defined above, to reduction reaction, followed by removing the protecting group, if necessary.

[0032] The reduction reaction may be carried out by a conventional method, for example, by reduction using a metal hydride, or by catalytic hydrogenation. The reduction with a metal hydride is carried out by using a metal hydride in a solvent, and the catalytic hydrogenation is carried out, for example, by using a catalyst under atmospheric pressure under hydrogen gas.

[0033] In the catalytic hydrogenation, the catalyst may be any conventional ones, for example, palladium-carbon, platinum oxide, and the like.

[0034] In the reduction using a metal hydride, the metal hydride may be any conventional ones which can reduce the double bond, especially ones which can reduce the double bond but not the ketone group, for example, sodium hydrogen telluride. Sodium hydrogen telluride may be prepared according to the method disclosed in Synthesis, p. 545 (1978), and usually used in an amount of 1 to 3 equivalents, preferably in an amount of 1 to 1.5 equivalent, to 1 equivalent of the chalcone derivative.

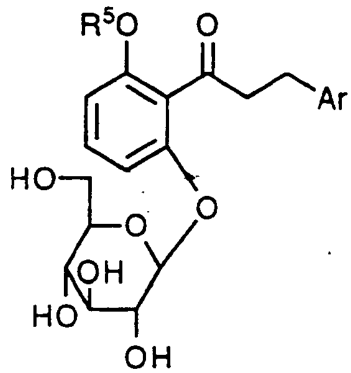
[0035] The solvent may be any inert solvents which do not affect the reaction, for example, organic solvents (e.g.

methanol, ethanol, tetrahydrofuran, ethyl acetate, acetic acid, etc.), or a mixture of water and these solvents.

[0036] The reaction may be carried out at a temperature from under cooling or with heating, preferably at a temperature from 10°C to 30°C.

[0037] Among the active compounds [I-A], the following compounds are prepared as follows:

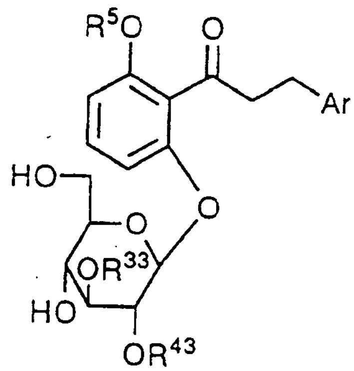
(1) The compound of the formula [I-c] may be prepared by acylating the 6-hydroxy group of the glucopyranosyl group of a compound of the formula [I-i]: .



[I-i]

wherein Ar and OR^5 are the same as defined above.

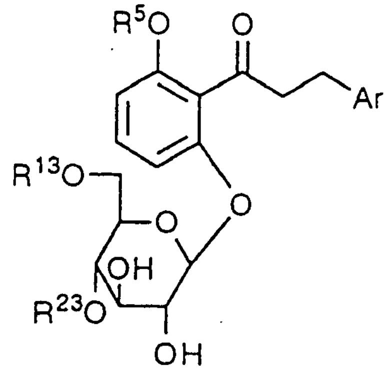
(2) The compound of the formula [I-d] may be prepared by acylating the 4- and 6-hydroxy groups of the glucopyranosyl group of the compound of the formula [I-j]:



[I-j]

wherein R^{33} and R^{43} are both a protecting group for hydroxy group, and Ar and OR^5 are the same as defined above, followed by removing the protecting groups.

(3) The compound of the formula [I-e] may be prepared by acylating the 2- and 3-hydroxy groups of the glucopyranosyl group of the compound of the formula [I-k]:



[I-k]

wherein R^{13} and R^{23} are both a protecting group for hydroxy group, and Ar and OR^5 are the same as defined above, followed by removing the protecting groups.

[0038] In the acylation reactions of the above (2) and (3), the protecting group for hydroxy group in the compound [I-j] and the compound [I-k] may be any conventional ones which can be a protecting group for hydroxy group, for example, in addition the protecting groups for the group of the formula: OR^5, benzyloxy group, a lower alkanoyl group, a lower alkoxycarbonyl group, and the like, or R^{13} and R^{23} may combine together to form benzylidene group, a lower alkoxy-substituted methylene group or a di-lower alkoxy-substituted methylene group.

[0039] In the acylation reactions in the above (1), (2), and (3); when the group of the formula: OR^5 in the starting compounds is a free hydroxy group, or Ar in the starting compounds is hydroxyphenyl group, these groups may also be acylated during the these acylation reactions, but the products thus obtained are also included in the desired compounds of the present invention.

[0040] The acylation of the starting compound is carried out by reacting the starting compound with an organic acid corresponding to the desired acyl group, or a salt thereof, or a reactive derivative thereof. The reaction with an acid compound corresponding to the desired acyl group may be carried out in the presence or absence of a condensing agent, and the reaction of the starting compound with a reactive derivative of the said compound is carried out in the presence or absence of an acid acceptor, in a solvent, respectively.

[0041] The salt of the organic acid includes, for example, an alkali metal salt and an alkaline earth metal salt such as sodium salt, potassium salt, calcium salt, and the like. The reactive derivative includes a halide, anhydride, an active ester of a corresponding acid.

[0042] The acid acceptor includes, for example, an inorganic base (e.g. an alkali metal hydroxide, an alkali metal carbonate, an alkali metal hydrogen carbonate, an alkali metal hydride, etc.) or an organic base (e.g. a tri-lower alkylamine, pyridine, 4-dimethylaminopyridine, etc.).

[0043] The condensing agent includes, for example, conventional ones such as phosphorus oxychloride, N,N'-carbonyldiimidazole, diethyl cyanophosphate, dicyclohexylcarbodiimide, and the like.

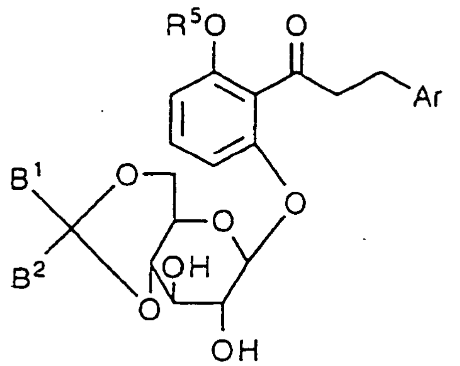
[0044] The solvent may be any conventional ones which do not affect disadvantageously the reaction, for example, dichloromethane, dimethylformamide, tetrahydrofuran, and the like.

[0045] The reaction is carried out under cooling or with heating, preferably at a temperature from -10°C to 100°C, more preferably at a temperature from 0°C to 50°C.

[0046] In the above reaction, the degree of the acylation, i.e. the acylation of all hydroxy groups or selective acylation of some hydroxy groups, may be selected by controlling the difference of stereo-structural circumstance around the hydroxy group of the starting compound, or the amount of the acid compound, a salt thereof or a reactive derivative thereof.

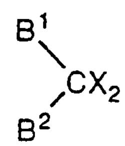
[0047] In addition, in the obtained products, when R^{12} to R^{42} or R^{14} to R^{44} are an acyl group having a protected amino group, or the group of the formula: OR^5 is a protected hydroxy group, these protecting groups may be removed, if necessary. The removal of these protecting groups may be carried by a conventional method such as hydrolysis, reduction, acid-treatment, etc., according to the types of the protecting groups to be removed.

[0048] The dihydrochalcone derivative of the formula [I-h]:



[I-h]

wherein B^1 and B^2 are the same and different and are each hydrogen atom, phenyl group, a lower alkanoyloxy group or a lower alkoxy group, or B^1 and B^2 may form a group of the formula: =O, and Ar and OR^5 are the same as defined above, may be prepared by reacting the compound of the formula [I-i] and a compound of the formula [III-a]:



[III-a]

wherein X is a reactive residue, and B^1 and B^2 are the same as defined above, or a compound of the formula [III-b]:

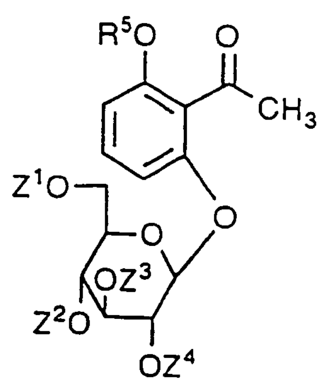
$$B^1\text{-CHO} \qquad [\text{III-b}]$$

wherein B^1 is the same as defined above.

[0049] The reaction of the compound [I-i] and the compound [III-a] or the compound [III-b] may be carried out in the presence of an acid catalyst, or in the presence of an acid acceptor, in a solvent. The acid catalyst includes, for example, Lewis acids (e.g. zinc chloride, etc.), mineral acids (e.g. hydrochloric acid, sulfuric acid, nitric acid, etc.), or organic acids (e.g. p-toluenesulfonic acid, methanesulfonic acid, etc.). The acid-acceptor includes, for example, inorganic bases (e.g. an alkali metal hydroxide, an alkali metal carbonate, an alkali metal hydrogen carbonate, an alkali metal hydride, etc.), or a tri-lower alkylamine, pyridine, 4-dimethylaminopyridine, and the like. The reaction is carried out under cooling or with heating, preferably at a temperature from 10°C to 40°C.

[0050] The solvent used in the above reactions may be any conventional ones which do not disadvantageously affect the reactions.

[0051] The starting compound of the formula [II] may be prepared by condensing an acetophenone derivative of the formula [IV]:



[IV]

wherein Z^1, Z^3 and Z^4 are a protected or unprotected hydroxy group, Z^2 is a protected or unprotected hydroxy group or α-D-glucopyranosyl group in which the hydroxy groups are protected, and OR^5 is the same as defined above, with an aldehyde compound of the formula [V]:

$$Ar^1\text{-CHO} \qquad [V]$$

wherein Ar^1 is the same as defined above, followed by removing the protecting groups, if necessary, further by acylating the hydroxy group of the product, or by reacting the product with the compound [III-a], or by reacting the product with the compound [III-b], if necessary.

[0052] The condensation reaction of the compound [IV] and the compound [V] may be carried out by a conventional method, for example, in the presence of a base (e.g. an alkali metal hydroxide, etc.) in a solvent (e.g. organic solvents such as methanol, ethanol, etc., or a mixture of water and these organic solvents) under cooling or with heating, preferably at a temperature from 10°C to 30°C.

[0053] In the starting compounds [IV], the "protected hydroxy group" includes hydroxy groups protected by a conventional protecting group such as a lower alkanoyl group, a substituted or unsubstituted phenyl-lower alkyl group, a tri-lower alkylsilyl group, etc. The removal of these protecting groups may be carried out by a conventional method such as hydrolysis, reduction, acid - treatment, etc.,which should be selected according to the types of the protecting groups to be removed. When said protecting group is a lower alkanoyl group such as acetyl group, the removal thereof may be advantageously carried out simultaneously with the condensation reaction in one step by using an alkali metal hydroxide.

[0054] Besides, in the condensation reaction for preparation of the compound [II], when hydroxybenzaldehyde is used as an aldehyde compound, the yield of the product is improved by the use of hydroxybenzaldehyde having phenolic hydroxy group protected.

[0055] In the above condensation reaction, the protecting group for phenolic hydroxy group of the aldehyde compound [V] may be any conventional ones which are easily removed by a conventional method such as hydrolysis, reduction, acid-treatment, and the like. More particularly, when the groups which are removed by reduction, i.e. substituted or unsubstituted phenyl-lower alkyl groups (e.g. benzyl group, etc.) are used as a protecting group, the removal of these protecting groups is advantageously carried out simultaneously with the reduction reaction of the chalcone derivative [II].

[0056] When the product is acylated after the condensation reaction, the acylation reaction may be carried out in the same procedures as in the reactions preparing the compounds [I-c] to [I-f]. When the product obtained by the condensation reaction and the compound [III-a] or the compound [III-b] are reacted, the reaction is carried out in the same procedures as the reaction preparing the compound [I-h].

[0057] The chalcone derivative [II] thus obtained may be used in the subsequent reduction reaction after purification, but used without further purification.

[0058] The compound of the formula [I-j] may be prepared, for example, by protecting the 2- and 3-hydroxy groups of the glucopyranosyl group of the compound [I-h] in which B^1 is phenyl group and B^2 is hydrogen atom, followed by removing substituents of the 4- and 6-hydroxy groups of the glucopyranosyl group.

[0059] The compound of the formula [I-k] may be prepared, for example, by protecting the 4 and 6-hydroxy groups of the glucopyranosyl group of the compound [I-j], followed by removing the protecting groups for the 2- and 3-hydroxy groups of the glucopyranosyl group.

[0060] In the above reactions, the protecting for the hydroxy groups of the glucopyranosyl group may be any ones which can be easily removed by a conventional method such as hydrolysis, reduction, acid-treatment, and the like.

[0061] The starting compound [IV] wherein Z^1 to Z^4 are acetyl group, may be prepared according to the method disclosed in Journal of Medicinal and Pharmaceutical Chemistry, Vol. 5, p. 1054 (1962), for example, by reacting 2',6'-dihydroxyacetophenone and 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide in the presence of potassium hydroxide in an aqueous acetone.

[0062] The starting compound [IV] wherein Z^1, Z^3 and Z^4 are acetyl group, and Z^2 is α-D-glucopyranosyl group in which the hydroxy group is protected by acetyl group may be prepared by refluxing 2',6'-dihydroxyacetophenone and 2,3,6-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-α-D-glucopyranosyl bromide in the presence of cadmium carbonate in toluene.

[0063] Among the active compounds [I], the compound of the formula [I] wherein Ar is 4-hydroxyphenyl group, 4-methoxyphenyl group or phenyl group, R^1, R^2, R^3 and R^4 are all hydrogen atom, and the group of the formula: OR^5 is hydroxy group may be prepared according to the method disclosed in Biochemistry, Vol. 8, p. 2067 (1969).

[0064] Throughout the present specification, the "lower alkyl group", the "lower alkoxy group" and the "lower alkylene group" mean ones having 1 to 6 carbon atoms, respectively, and the "lower alkanoyl group" means ones having 2 to 7 carbon atoms, and "2'-O-(β-D-glucopyranosyl)" means "2-(β-D-glucopyranosyl)oxy".

Effects

[Pharmacological experiments]

Experiment 1: Hypoglycemic activity in mice (1)

Method:

[0065] After an overnight fast, a test compound (100 mg/kg) was orally administered to male diabetic KK mice (6 mice/group, 15 wk old), and immediately, glucose in isotonic saline (2 g/5 ml/kg) was subcutaneously administered to the mice. Blood was collected from tail tip without anesthesia after a fixed time, and the blood glucose concentration was measured by glucose • oxidase method. In the control group, the same procedures were repeated except a solvent was administered instead of a test compound.

[0066] The results are shown in Table 1.

Test compound:

[0067] 2'-O-(β-D-glucopyranosyl)-6'-hydroxy-4-methoxydihydrochalcone [i.e. 2'-(β-D-glucopyranosyl)oxy-6'-hydroxy-4-methoxydihydrochalcone]

Table 1

Time (hr)	Blood glucose (mg/dl)*	
	Tested group	Control
0 (before administration)	255±17	254±18
0.5	344±18	535±23
1	359±15	612±5
2	333±17	520±17

(*: average ± standard deviation)

[0068] As is shown in the above results, the blood glucose concentration is significantly decreased in the tested group as compared with that of the control group.

Experiment 2: Hypoglycemic activity in mice (2)

Method:

[0069] After an overnight fast, a test compound (100 mg/kg) was orally administered to male ddY-mice (6 mice/group, 8 wk old), and immediately, glucose in isotonic saline (1 g/5 ml/kg) was subcutaneously administered to the mice. After a fixed time therefrom, blood was collected from tail tip without anesthesia, and the blood glucose concentration therein was measured by glucose • oxidase method. In the control group, glucose was administered subcutaneously to the mice without a test compound.

[0070] The results are shown in Table 2.

Test compound:

[0071] 2'-O-(2,3-di-O-acetyl-β-D-glucopyranosyl)-6'-hydroxy-4-methoxyldihydrochalcone

Table 2

Time (hr)	Blood glucose (mg/dl)*	
	Tested group	Control
0 (before administration)	80±3	85±5
0.5	139±4	201±14
1	117±9	158±16
2	87±7	94±9

(*: average ± standard deviation)

[0072] As is shown in the above results, the blood glucose concentration in the tested group was significantly decreased as compared with that of the control group.

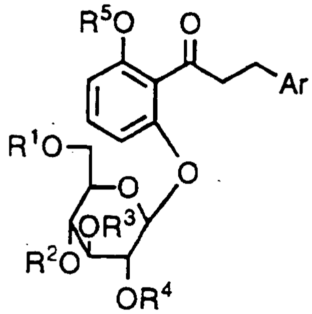
Experiment 3: Urine glucose increasing activity in rats

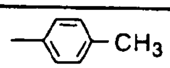
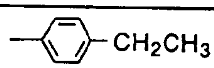
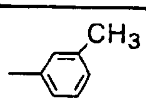
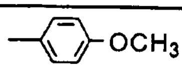
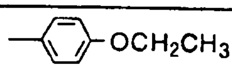
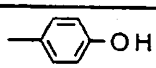
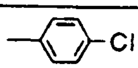
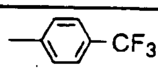
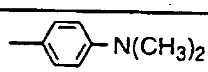
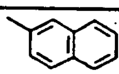
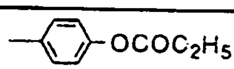
Method:

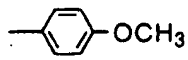
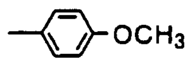
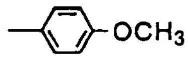
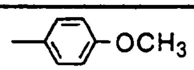
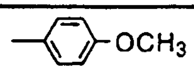
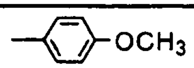
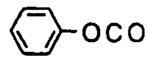
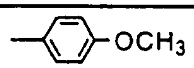
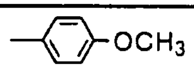
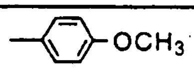
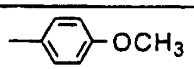
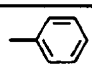
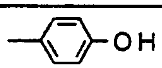
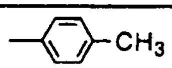
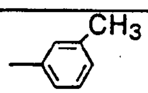
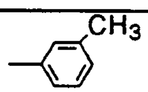
[0073] A test compound solution (100 mg/5 ml/kg) was orally administered twice at 8-hr intervals to male SD-rats (3 to 5 rats/group, 6 wk old). The test compound solution was prepared by adding Tween 80 to a test compound, which was suspended into purified water. In the control group, purified water containing only Tween 80 was administered instead of the test compound solution. Rats were housed individually into a metabolite cage, and urine was collected for 24 hours after the first administration of the test compound. After measuring the urine volume, the urine was centrifuged in order to remove the impurity, and the urine glucose concentration therein was determined by glucose • analyzer (Appek Co. Ltd.). The amount of the urine glucose (mg) excreted for 24 hours was determined according to the urine volume (ml) and the urine glucose concentration therein (mg/ml). The amount of urine glucose excreted for 24 hours was in the range of 0 to 6 mg in the control group, and that of the phlorizin treated group was 11±6 mg.

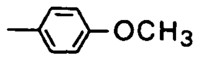
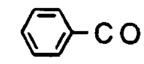
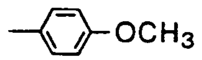
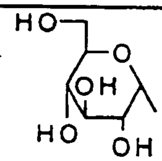
[0074] The results are shown in Table 3.

Table 3



Test Compound					Urine glucose (mg/24 hr)
Ar	R^1	R^2	R^3, R^4	R^5	
	H	H	H	H	344±84
	H	H	H	H	277±64
	H	H	H	H	299±35
	H	H	H	H	380±52
	H	H	H	H	124±27
	H	H	H	H	60±9
	H	H	H	H	253±23
	H	H	H	H	217±18
	H	H	H	H	114±21
	H	H	H	H	178±22
	H	H	H	H	224±36
	H	H	H	H	165±12

	H	H	CH_3CO	CH_3CO	352±62
	H	H	CH_3CO	H	421±45
	H	H	CH_3OCH_2CO	H	446±54
	H	H	CH_3CH_2O - CH_2CO	H	417±17
	H	H	CH_3CH_2OCO	H	255±36
	H	H		H	195±41
	H	H	$CH_3SO_3H{\cdot}NH_2$ - CH_2CO	H	194±35
	H	H	$(CH_3)_2CH$ - CH_2OCH_2CO	H	218±33
	H	H	$CH_3O(CH_2)_2$ - CO	H	213±31
	H	H	$CH_3O(CH_3)$ - CHCO	H	282±46
	H	H	CH_3CO	H	265±126
	H	H	CH_3OCH_2CO	H	251±16
	H	H	CH_3OCH_2CO	H	122±49
	H	H	CH_3OCH_2CO	H	289±83
	H	H	CH_3CO	H	172±22
	H	H	CH_3CH_2O - CH_2CO	H	352±88

		H	H	H	214±44
	H		H	H	157±15

[0075] As is shown in the above results, the active dihydrochalcone derivatives [I] of the present invention show about 5 to 40 times as strong urine glucose increasing activity as phlorizin does.

Examples

[0076] The present invention is illustrated in more detail by the following Examples and Reference Examples, but should not be construed to be limited thereto.

Example 1

[0077]

(1) To a mixture of 2'-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl) - 6'-hydroxyacetophenone [i.e. 2'-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)oxy - 6'-hydroxyacetophenone] (1000 mg), p-tolualdehyde (373 mg) and ethanol (10 ml) is added dropwise a 50 % aqueous potassium hydroxide solution (2 ml), and the mixture is stirred at room temperature overnight. The mixture is evaporated under reduced pressure to remove the solvent, and to the residue are added water and diethyl ether. The mixture is stirred and the aqueous layer is collected. The aqueous layer is neutralized with a 10 % hydrochloric acid under ice-cooling, and extracted with ethyl acetate. The extract is washed with water, dried, and evaporated to remove the solvent to give crude 2'-O-(β-D - glucopyranosyl)-6'-hydroxy-4-methylchalcone (670 mg).

FABMS (m/z): 417 (MH^+)

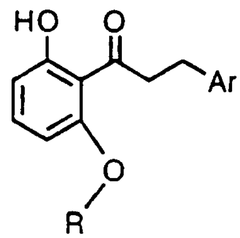
(2) The above crude 2'-O-(β-D-glucopyranosyl)-6'-hydroxy-4 - methylchalcone (665 mg) is dissolved in ethanol (20 ml), and the mixture is subjected to catalytic hydrogenation under atmospheric pressure by using 10 % palladium-carbon (0.5 g). The catalyst is removed by filtration, and the filtrate is concentrated under reduced pressure. The residue is purified by silica gel column chromatography to give 2'-O-(β-D-glucopyranosyl)-6'-hydroxy-4-methyldihydrochalcone (470 mg).

M.p. 109-111°C
NMR (DMSO-d_6) δ : 2.25 (3H, s), 2.85 (2H, t, J=7.6 Hz), 3.0-3.4 (6H, m), 3.45 (1H, m), 3.70 (1H, dd, J=5.4, 10.3 Hz), 4.53 (1H, t, J=5.6 Hz), 4.91 (1H, d, J=7.3 Hz), 5.01 (1H, d, J=4.9 Hz), 5.07 (1H, d, J=4.4 Hz), 5.19 (1H, d, J=4.9 Hz), 6.55 (1H, d, J=7.8 Hz), 6.68 (1H, d, J=8.3 Hz), 7.05 (2H, d, J=7.8 Hz), 7.14 (2H, d, J=7.8 Hz), 7.24 (1H, t, J=8.3 Hz), 11.01 (1H, brs)
IR (nujol) cm^{-1}: 3440, 3320, 1620
FABMS (m/z): 441 [$(M+Na)^+$]

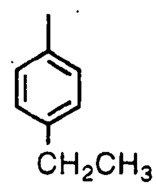
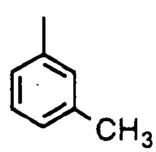
Examples 2-30

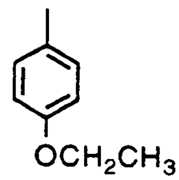
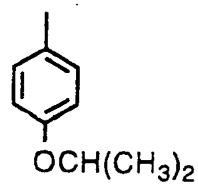
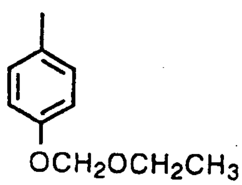
[0078] Using the corresponding starting compounds, the compounds listed in Table 4 are obtained in the same manner as in Example 1.

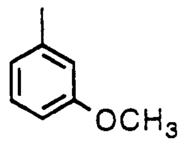
Table 4



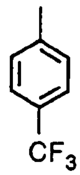
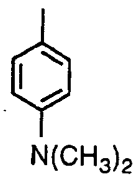
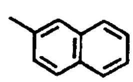
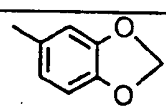
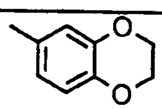
(R: β-D-glucopyranosyl group)

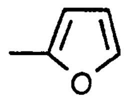
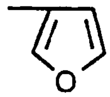
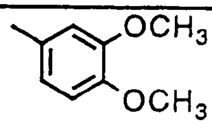
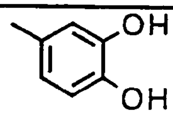
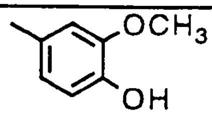
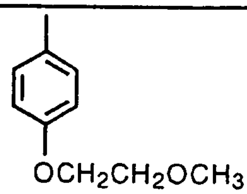
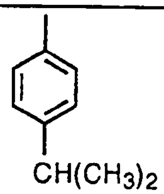
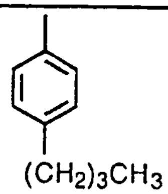
Ex. No.	Ar	Physical properties
2		M.p. 127-129.5°C NMR (DMSO-d_6) δ : 1.15 (3H, t, J=7.8 Hz), 2.5-2.6 (2H, m), 2.86 (2H, t, J=7.3 Hz), 3.1-3.4 (6H, m), 3.47 (1H, dd, J=5.4, 11.5 Hz), 3.70 (1H, dd, J=5.4, 10.3 Hz), 4.56 (1H, t, J=11.7 Hz), 4.91 (1H, d, J=7.3 Hz), 5.03 (1H, d, J=4.9 Hz), 5.10 (1H, d, J=4.4 Hz), 5.23 (1H, d, J=5.4 Hz), 6.55 (1H, d, J=7.8 Hz), 6.67 (1H, d, J=8.3 Hz), 7.08 (2H, d, J=8.3 Hz), 7.16 (2H, d, J=8.3 Hz), 7.24 (1H, t, J=8.3 Hz), 10.99 (1H, br) IR (nujol) cm^{-1}: 3600-3200, 1620, 1600, 1460, 1380, 1230 FABMS (m/z): 455 [$(M+Na)^+$]
3		M.p. 78-81°C NMR (DMSO-d_6) δ : 2.27 (3H, s), 2.86 (2H, t, J=7.4 Hz), 3.14-3.28 (6H, m), 3.45 (1H, dd, J=5.9, 11.8 Hz), 3.70 (1H, dd, J=5.2, 10.3 Hz), 4.57 (1H, t, J=5.6 Hz), 4.91 (1H, d, J=7.5 Hz), 5.04 (1H, d, J=5.2 Hz), 5.11 (1H, d, J=4.7 Hz), 5.23 (1H, d, J=5.2 Hz), 6.55 (1H, d, J=8.1 Hz), 6.68 (1H, d, J=8.5 Hz), 6.97 (1H, d, J=7.6 Hz), 7.04 (1H, d, J=7.9 Hz), 7.07 (1H, s), 7.14 (1H, t, J=7.5 Hz), 7.24(1H, t, J=8.3 Hz), 10.99 (1H, s) IR (nujol) cm^{-1}: 3600-3200, 1620, 1600, 1460, 1220 FABMS (m/z): 441 [$(M+Na)^+$]

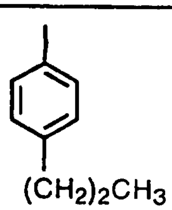
4		M.p. 76.5-78°C NMR (DMSO-d_6) δ : 1.30 (3H, t, J=7.1 Hz), 2.83 (2H, t, J=7.3 Hz), 3.1-3.4 (6H, m), 3.47 (1H, m), 3.70 (1H, dd, J=5.4, 10.3 Hz), 3.97 (2H, q, J=7.1 Hz), 4.56 (1H, t, J=5.6 Hz), 4.91 (1H, d, J=7.3 Hz), 5.03 (1H, d, J=4.9 Hz), 5.10 (1H, d, J=4.4 Hz), 5.23 (1H, d, J=4.9 Hz), 6.55 (1H, d, J=8.3 Hz), 6.67 (1H, d, J=8.3 Hz), 6.80 (2H, d, J=8.8 Hz), 7.15 (2H, d, J=8.3 Hz), 7.24 (1H, t, J=8.3 Hz), 10.99 (1H, s) IR (nujol) cm^{-1}: 3560, 3500, 3440, 3340, 1630 FABMS (m/z): 471 [$(M+Na)^+$]
5		M.p. 82-85°C NMR (DMSO-d_6) δ : 1.23 (6H, t, J=5.9 Hz), 2.82 (2H, t, J=7.6 Hz), 3.1-3.4 (6H, m), 3.46 (1H, m), 3.70 (1H, dd, J=5.4, 10.3 Hz), 4.52 (1H, q, J=5.9 Hz), 4.56 (1H, t, J=5.9 Hz), 4.91 (1H, d, J=7.3 Hz), 5.03 (1H, d, J=4.9 Hz), 5.10 (1H, d, J=4.4 Hz), 5.23 (1H, d, J=5.4 Hz), 6.55 (1H, d, J=8.3 Hz), 6.67 (1H, d, J=8.3 Hz), 6.78 (2H, ddd, J=2.0, 2.9, 8.8 Hz), 7.14 (2H, dd, J=2.7, 8.8 Hz), 7.24 (1H, t, J=8.3 Hz), 10.98 (1H, s) IR (nujol) cm^{-1}: 3400, 1630 FABMS (m/z): 485 [$(M+Na)^+$]
6		Foam NMR (DMSO-d_6) δ : 1.12 (3H, t, J=7.1 Hz), 2.84 (2H, t, J=7.3 Hz), 3.0-3.4 (6H, m), 3.45 (1H, m), 3.63 (2H, q, J=7.1 Hz), 3.65 (1H, m), 4.56 (1H, t, J=5.6 Hz), 4.91 (1H, d, J=7.3 Hz), 5.03 (1H, d, J=4.9 Hz), 5.10 (1H, d, J=4.4 Hz), 5.17 (2H, s), 5.24 (1H, d, J=4.9 Hz), 6.55 (1H, d, J=8.3 Hz), 6.67 (1H, d, J=8.3 Hz), 6.90 (2H, ddd, J=2.0, 2.4, 8.8 Hz), 7.17 (2H, d, J=8.8 Hz), 7.24 (1H, t, J=8.3 Hz), 10.98 (1H, s) IR (nujol) cm^{-1}: 3400, 1630 FABMS (m/z): 501 [$(M+Na)^+$]

7		M.p. 105-107°C NMR (DMSO-d_6) δ : 2.88 (2H, t, J=7.3 Hz), 3.2-3.6 (6H, m), 3.47 (1H, dd, J=5.9, 11.5 Hz), 3.6-3.8 (4H, m), 4.56 (1H, t, J=5.9 Hz), 4.91 (1H, d, J=6.8 Hz), 5.03 (1H, d, J=5.4 Hz), 5.10 (1H, d, J=4.4 Hz), 5.23 (1H, d, J=4.9 Hz), 6.55 (1H, d, J=7.8 Hz), 6.68 (1H, d, J=8.3 Hz), 6.7-6.8 (3H, m), 7.1-7.3 (2H, m), 11.00 (1H, s) IR (nujol) cm^{-1}: 3600-3000, 1630, 1600, 1260, 1220 FABMS (m/z): 457 [$(M+Na)^+$]
8 *		M.p. 142-144°C NMR (DMSO-d_6) δ : 2.90 (2H, t, J=7.3 Hz), 3.1-3.4 (6H, m), 3.45 (1H, m), 3.70 (1H, dd, J=4.9, 11.2 Hz), 4.57 (1H, t, J=5.4 Hz), 4.91 (1H, d, J=6.8 Hz), 5.04 (1H, d, J=3.9 Hz), 5.11 (1H, bro), 5.26 (1H, d, J=4.4 Hz), 6.55 (1H, d, J=8.3 Hz), 6.68 (1H, d, J=8.3 Hz), 7.24 (1H, t, J=8.3 Hz), 7.30 (4H, s), 10.95 (1H, bro) IR (nujol) cm^{-1}: 3400, 1630 FABMS (m/z): 463, 461 [$(M+Na)^+$]
9		M.p. 156-158°C NMR (DMSO-d_6) δ : 2.91 (2H, t, J=7.3 Hz), 3.1-3.4 (6H, m), 3.44 (1H, dd, J=5.9, 11.2 Hz), 3.70 (1H, dd, J=5.4, 9.8 Hz), 4.56 (1H, t, J=5.9 Hz), 4.91 (1H, d, J=7.3 Hz), 5.03 (1H, d, J=4.9 Hz), 5.10 (1H, d, J=4.4 Hz), 5.24 (1H, d, J=5.4 Hz), 6.54 (1H, d, J=7.8 Hz), 6.67 (1H, d, J=8.3 Hz), 7.0-7.1 (2H, m), 7.2-7.3 (3H, m), 10.94 (1H, s) IR (nujol) cm^{-1}: 3600-3200, 1620, 1600, 1460, 1240, 1220 FABMS (m/z): 445 [$(M+Na)^+$], 423 (MH^+)

*: Acetic acid is used as a solvent in the reduction reaction.

10		M.p. 171-173°C NMR (DMSO-d_6) δ : 3.00 (2H, t, J=7.3 Hz), 3.10 - 3.60 (7H, m), 3.70 (1H, dd, J=5.4, 10.26 Hz), 4.57 (1H, t, J=5.9 Hz), 4.91 (1H, d, J=7.3 Hz), 5.04 (1H, d, J=4.9 Hz), 5.11 (1H, d, J=4.4 Hz), 5.28 (1H, d, J=5.4 Hz), 6.55 (1H, d, J=7.8 Hz), 6.68 (1H, d, J=8.3 Hz), 7.24 (1H, dd, J=7.8, 8.3 Hz), 7.50, 7.61 (2H, each d, J=8.3 Hz), 10.92 (1H, s) IR (nujol) cm^{-1}: 1620 FABMS (m/z): 495 [(M+Na)+]
11		M.p. 71°C ~ (gradually melting) NMR (DMSO-d_6) δ : 2.75-2.85 (2H, m), 2.83 (6H, s), 3.47 (1H, dd, J=5.8, 11.8 Hz), 3.70 (1H, dd, J=5.4, 10.3 Hz), 4.56 (1H, t, J=5.9 Hz), 4.91 (1H, d, J=7.3 Hz), 5.03 (1H, d, J=5.4 Hz), 5.10 (1H, d, J=4.4 Hz), 5.21 (1H, d, J=4.9 Hz), 6.56-6.69 (4H, m), 7.14 (2H, d, J=8.3 Hz), 7.24 (1H, t, J=8.3 Hz), 11.03 (1H, s) IR (nujol) cm^{-1}: 3600-3200, 1620, 1600, 1520, 1460, 1230 FABMS (m/z): 448 [(M+Na)+]
12		M.p. 97-100°C NMR (DMSO-d_6) δ : 3.08 (2H, t, J=7.3 Hz), 3.1-3.4 (7H, m), 3.71 (1H, dd, J=6.4, 10.8 Hz), 4.58 (1H, t, J=5.4 Hz), 4.94 (1H, d, J=7.3 Hz), 5.04 (1H, d, J=4.9 Hz), 5.11 (1H, d, J=4.4 Hz), 5.29 (1H, d, J=5.4 Hz), 6.56 (1H, d, J=8.3 Hz), 6.64 (1H, d, J=8.3 Hz), 7.25 (1H, t, J=8.3 Hz), 7.38-7.48 (3H, m), 7.76-7.88 (4H, m), 11.01 (1H, s) IR (nujol) cm^{-1}: 3600-3200, 1630, 1600, 1460, 1230 FABMS (m/z): 477 [(M+Na)+]
13		M.p. 168.5-170°C IR (nujol) cm^{-1}: 3550, 3520, 3440, 3380, 1620 FABMS (m/z): 471 [(M+Na)+]
14		M.p. 86°C ~ (gradually melting) IR (nujol) cm^{-1}: 3400, 1630 FABMS (m/z): 485 [(M+Na)+]

15		M.p. 154-156°C IR (nujol) cm^{-1}: 3560, 3440, 3400, 1620, 1600 FABMS (m/z): 417 [$(M+Na)^+$]
16		M.p. 65°C ~ (gradually melting) IR (nujol) cm^{-1}: 3600-3000, 1630, 1600, 1230 FABMS (m/z): 417 [$(M+Na)^+$]
17		M.p. 176-178.5°C IR (nujol) cm^{-1}: 3560, 3490, 3460, 1620 FABMS (m/z): 465 (MH^+), 464 (M^+)
18		M.p. 78-80°C (decomposed) IR (nujol) cm^{-1}: 3380, 1630 FABMS (m/z): 437 (MH^+), 436 (M^+)
19		M.p. 149-150.5°C IR (nujol) cm^{-1}: 3480, 3420, 3360, 3300, 1620 FABMS (m/z): 437 [$(M+Na)^+$]
20		M.p. 56°C ~ (gradually melting) IR (nujol) cm^{-1}: 3360, 1630 FABMS (m/z): 501 [$(M+Na)^+$]
21		M.p. 109-112°C IR (nujol) cm^{-1}: 3600-3200, 1630, 1610, 1230 FABMS (m/z): 469 [$(M+Na)^+$]
22		Amorphous powders IR (nujol) cm^{-1}: 3400, 3320, 1625, 1600 FABMS (m/z): 483 [$(M+Na)^+$]

23		Amorphous powders IR (nujol) cm^{-1}: 3440, 3320, 1625, 1600 FABMS (m/z): 469 [$(M+Na)^+$]

Examples 24

[0079]

(1) To dimethylformamide (50 ml) are added 2'-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-6'-hydroxyacetophenone (4.82 g) and potassium carbonate (4.14 g), and thereto is added dropwise benzyl bromide (2.56 g) with stirring. The mixture is stirred at room temperature for 2 hours. The reaction mixture is concentrated under reduced pressure, and to the residue are added ethyl acetate and water. The mixture is stirred and the organic layer is collected. The organic layer is washed with water, dried, and evaporated to remove the solvent. The residue is purified by silica gel column chromatography to give 6'-benzyloxy-2'-O-(2,3,4,6-tetra-O-acetyl-β-D-gluco - pyranosyl)acetophenone (3.2 g).

IR (nujol) cm^{-1}: 1760, 1700, 1600
FABMS (m/z): 595 [$(M+Na)^+$]

(2) To ethanol (30 ml) are added 6'-benzyloxy-2'-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)acetophenone (2.9 g) and 4-tetrahydropyranyl-oxybenzaldehyde (1.56 g), and thereto is added dropwise a 50 % aqueous potassium hydroxide solution (3 ml) with stirring. The mixture is treated in the same manner as in Example 1-(1), and the resulting crude product is dissolved in a mixture of acetic acid-water-tetrahydrofuran (2:1:2) (50 ml). The mixture is heated at 50°C for three hours, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography to give 6'-benzyloxy-2'-O-(β-D-glucopyranosyl)-4-hydroxychalcone (1.20 g).

IR (nujol) cm^{-1}: 3600-3200, 1660, 1600, 1260
FABMS (m/z): 531 [$(M+Na)^+$]

(3) 6'-Benzyloxy-2'-O-(β-D-glucopyranosyl)-4-hydroxychalcone (0.79 g) and triethylamine (0.19 g) are dissolved in dimethylacetoamide (30 ml), and thereto is added dropwise with stirring ethyl chlorocarbonate (0.20 g) under ice-cooling. The mixture is stirred at room temperature for one hour, and thereto are added ethyl acetate and water, and the mixture is stirred. The organic layer is collected, and washed with water, dried, and evaporated to remove the solvent. The residue is purified by silica gel column chromatography to give 6'-benzyloxy-4-ethoxycarbonyloxy-2'-O-(β-D-glucopyranosyl)chalcone (0.73 g).

FABMS (m/z): 603 [$(M+Na)^+$]

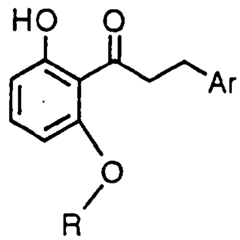
(4) 6'-Benzyloxy-4-ethoxycarbonyloxy-2'-O-(β-D-glucopyranosyl)-chalcone (0.70 g) is treated in the same manner as in Example 1-(2) to give 4-ethoxycarbonyl-2'-O-(β-D-glucopyranosyl)-6'-hydroxydihydrochalcone (0.48 g).

M.p. 65°C ~ (gradually melting)
NMR ($DMSO-d_6$) δ : 1.28 (3H, t, J=7.1 Hz), 2.92 (2H, t, J=7.1 Hz), 3.1-3.3 (6H, m), 3.4-3.5 (1H, m), 3.6-3.7 (1H, m), 4.23 (2H, q, J=7.1 Hz), 4.57 (1H, t, J=5.7 Hz), 4.91 (1H, d, J=7.3 Hz), 5.03 (1H, d, J=5.3 Hz), 5.10 (1H, d, J=4.7 Hz), 5.27 (1H, d, J=5.2 Hz), 6.55 (1H, d, J=8.2 Hz), 6.68 (1H, d, J=8.3 Hz), 7.10 (2H, d, J=8.6 Hz), 7.24 (1H, t, J=8.3 Hz), 7.31 (2H, d, J=8.6 Hz), 10.94 (1H, s)
IR (nujol) cm^{-1}: 3600-3200, 1760, 1720, 1630, 1600
FABMS (m/z): 515 [$(M+Na)^+$]

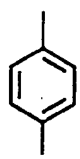
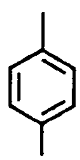
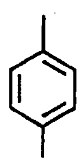
Examples 25-36

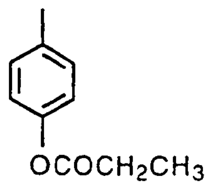
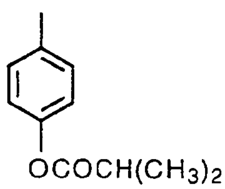
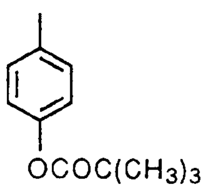
[0080] Using the corresponding starting compounds, the compounds listed in Table 5 are obtained in the same manner as in Example 24.

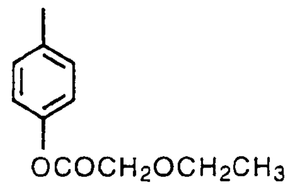
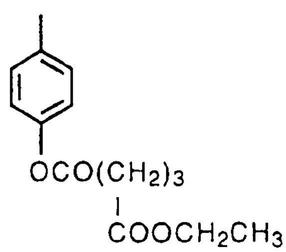
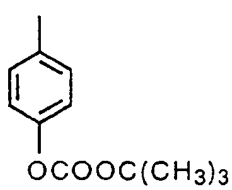
Table 5

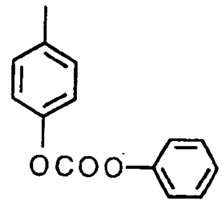
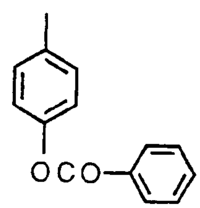
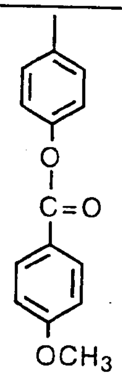


(R: β-D-glucopyranosyl group)

Ex. No.	Ar	Physical properties
25	 $OCOOCH_2CH(CH_3)_2$	Amorphous powders IR (nujol) cm^{-1}: 3360, 1760, 1740, 1630 FABMS (m/z): 543 [$(M+Na)^+$]
26	 $OCOO(CH_2)_2OCH_3$	Amorphous powders IR (nujol) cm^{-1}: 3340, 1760, 1630 FABMS (m/z): 545 [$(M+Na)^+$]
27	 $OCOCH_3$	M.p. 56°C ~ (gradually melting) NMR (DMSO-d_6) δ : 2.24 (3H, s), 2.91 (2H, t, J=7.5 Hz), 3.11-3.37 (6H, m), 3.46 (1H, m), 3.70 (1H, ddd, J=1.8, 5.3,11.5 Hz), 4.56 (1H, t, J=5.7 Hz), 4.91 (1H, d, J=7.3 Hz), 5.02 (1H, t, J=5.2 Hz), 5.09 (1H, d, J=4.7 Hz), 5.26 (1H, d, J=5.3 Hz), 6.55 (1H, d, J=8.1 Hz), 6.68 (1H, d, J=8.1 Hz), 7.00 (2H, ddd, J=2.0, 2.7, 8.5 Hz), 7.24 (1H, t, J=8.3 Hz), 7.29 (2H, dd, J=2.1, 8.6 Hz), 10.95 (1H, s) FABMS (m/z): 485 [$(M+Na)^+$]

28		M.p. 48°C ~ (gradually melting) NMR (DMSO-d_6) δ : 1.12 (3H, t, J=7.5 Hz), 2.57 (2H, q, J=7.5 Hz), 2.91 (2H, t, J=7.4 Hz), 3.11-3.37 (6H, m), 3.46 (1H, m), 3.70 (1H, ddd, J=1.7, 5.2, 11.7 Hz), 4.56 (1H, t, J=5.7 Hz), 4.91 (1H, d, J=7.3 Hz), 5.02 (1H, d, J=5.3 Hz), 5.09 (1H, d, J=4.7 Hz), 5.26 (1H, d, J=5.2 Hz), 6.55 (1H, d, J=8.1 Hz), 6.68 (1H, d, J=8.4 Hz), 7.00 (2H, ddd, J=2.0, 2.7, 8.5 Hz), 7.24 (1H, t, J=8.3 Hz), 7.29 (2H, dd, J=2.0, 8.6 Hz), 10.96 (1H, s) FABMS (m/z): 499 [$(M+Na)^+$]
29		Foam NMR (DMSO-d_6) δ : 1.22 (6H, t, J=7.0 Hz), 2.79 (1H, sev., J=7.0 Hz), 2.91 (2H, t, J=7.5 Hz), 3.11-3.37 (6H, m), 3.46 (1H, m), 3.70 (1H, m), 4.56 (1H, t, J=5.6 Hz), 4.91 (1H, d, J=7.4 Hz), 5.02 (1H, d, J=5.1 Hz), 5.09 (1H, d, J=4.3 Hz), 5.26 (1H, d, J=5.1 Hz), 6.55 (1H, d, J=7.7 Hz), 6.68 (1H, d, J=8.0 Hz), 6.99 (2H, ddd, J=2.0, 2.8, 8.5 Hz), 7.24 (1H, t, J=8.3 Hz), 7.29 (2H, ddd, J=2.1, 2.7, 8.5 Hz), 10.97 (1H, s) FABMS (m/z): 513 [$(M+Na)^+$]
30		Foam NMR (DMSO-d_6) δ : 1.29 (9H, s), 2.91 (2H, t, J=7.3 Hz), 3.11-3.37 (6H, m), 3.46 (1H, m), 3.70 (1H, ddd, J=1.7, 5.2, 11.6 Hz), 4.56 (1H, t, J=5.7 Hz), 4.91 (1H, d, J=7.4 Hz), 5.02 (1H, d, J=5.2 Hz), 5.09 (1H, d, J=4.7 Hz), 5.26 (1H, d, J=5.2 Hz), 6.55 (1H, dd, J=0.8, 8.4 Hz), 6.68 (1H, d, J=7.9 Hz), 6.97 (2H, ddd, J=2.0, 2.7, 8.6 Hz), 7.25 (1H, t, J=8.3 Hz), 7.29 (2H, dd, J=2.0, 8.6 Hz), 10.99 (1H, s) FABMS (m/z): 527 [$(M+Na)^+$]

31		Foam NMR (DMSO-d_6) δ : 1.16 (3H, t, J=7.0 Hz), 2.91 (2H, t, J=7.4 Hz), 3.12-3.38 (6H, m), 3.46 (1H, m), 3.59 (2H, q, J=7.0 Hz), 3.70 (1H, ddd, J=1.8, 5.4, 11.5 Hz), 4.35 (2H, s), 4.56 (1H, t, J=5.8 Hz), 4.91 (1H, d, J=7.4 Hz), 5.02 (1H, t, J=5.2 Hz), 5.09 (1H, d, J=4.7 Hz), 5.26 (1H, d, J=5.2 Hz), 6.55 (1H, d, J=8.1 Hz), 6.68 (1H, d J=8.3 Hz), 7.04 (2H, ddd, J=2.0, 2.7, 8.6 Hz), 7.24 (1H, t, J=8.3 Hz), 7.31 (2H, ddd, J=2.0, 2.7, 8.6 Hz), 10.95 (1H, s) FABMS (m/z): 529 [$(M+Na)^+$]
32		NMR (DMSO-d_6) δ : 1.19 (3H, t, J=7.1 Hz), 1.87 (2H, quint, J=7.4 Hz), 2.41 (2H, t, J=7.3 Hz), 2.61 (2H, t, J=7.4 Hz), 2.91 (2H, t, J=7.5 Hz), 3.11-3.37 (6H, m), 3.46 (1H, m), 3.70 (1H, ddd, J=1.6, 5.2, 11.7 Hz), 4.07 (2H, q, J=7.1 Hz), 4.55 (1H, t, J=5.6 Hz), 4.91 (1H, d, J=7.3 Hz), 5.02 (1H, d, J=5.3 Hz), 5.08 (1H, d, J=4.6 Hz), 5.26 (1H, d J=5.1 Hz), 6.55 (1H, d, J=8.3 Hz), 6.68 (1H, d, J=8.4 Hz), 7.00 (2H, ddd, J=1.8, 2.5, 8.5 Hz), 7.24 (1H, t, J=8.3 Hz), 7.29 (2H, d, J=8.5 Hz), 10.96 (1H, s) FABMS (m/z): 585 [$(M+Na)^+$]
33		NMR (DMSO-d_6) δ : 1.48 (9H, s), 2.91(2H, t, J=7.3 Hz), 3.1-3.5 (7H, m), 3.70 (1H, dd, J=5.2, 11.5 Hz), 4.57 (1H, t, J=5.6 Hz), 4.91 (1H, d, J=7.3 Hz), 5.03 (1H, d, J=4.9 Hz), 5.10 (1H, d, J=3.9 Hz), 5.27 (1H, d, J=4.9 Hz), 6.55 (1H, d, J=7.8 Hz), 6.68 (1H, d, J=8.3 Hz), 7.06 (2H, d, J=8.8 Hz), 7.24 (1H, t, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz),10.96 (1H, s) FABMS (m/z): 543 [$(M+Na)^+$]

34		NMR (DMSO-d_6) δ : 2.93(2H, t, J=7.3 Hz), 3.12 - 3.37 (6H, m), 3.46 (1H, m), 3.70 (1H, ddd, J=1.6, 5.3, 11.7 Hz), 4.56 (1H, t, J=5.7 Hz), 4.91 (1H, d, J=7.3 Hz), 5.02 (1H, d, J=5.2 Hz), 5.10 (1H, d, J=4.7 Hz), 5.27 (1H, d, J=5.1 Hz), 6.55 (1H, d, J=8.1 Hz), 6.68 (1H, d, J=8.4 Hz), 7.24 (1H, t, J=8.3 Hz), 7.25 (2H, dd, J=2.1, 8.5 Hz), 7.29-7.39 (5H, m), 7.47 (2H, m), 10.95 (1H, s) FABMS (m/z): 563 [(M+Na)+]
35		NMR (DMSO-d_6) δ : 2.95 (2H, t, J=7.3 Hz), 3.12-3.38 (6H, m), 3.47 (1H, m), 3.71 (1H, ddd, J=1.7, 5.3, 11.8 Hz), 4.57 (1H, t, J=5.7 Hz), 4.92 (1H, d, J=7.3 Hz), 5.02 (1H, d, J=5.2 Hz), 5.10 (1H, d, J=4.6 Hz), 5.28 (1H, d, J=5.2 Hz), 6.56 (1H, d, J=7.8 Hz), 6.69 (1H, d, J=8.1 Hz), 7.17 (2H, ddd, J=2.0, 2.6, 8.5 Hz), 7.25 (1H, t, J=8.3 Hz), 7.36 (2H, ddd, J=1.9, 2.6, 8.5 Hz), 7.61 (2H, m), 7.75 (1H, m), 8.13 (2H, m), 10.98 (1H, s) FABMS (m/z): 547 [(M+Na)+]
36		NMR (DMSO-d_6) δ : 2.94 (2H, t, J=7.3 Hz), 3.12-3.38 (6H, m), 3.47 (1H, m), 3.71 (1H, ddd, J=1.7, 5.2, 11.4 Hz), 3.87 (3H, s), 4.57 (1H, t, J=5.6 Hz), 4.92 (1H, d, J=7.3 Hz), 5.02 (1H, d, J=5.3 Hz), 5.09 (1H, d, J=4.7 Hz), 5.27 (1H, d, J=5.1 Hz), 6.56 (1H, d, J=8.1 Hz), 6.69 (1H, d, J=8.4 Hz), 7.12 (2H, dd, J=2.1, 9.0 Hz), 7.13 (2H, dd, J=1.9, 8.5 Hz), 7.25 (1H, t, J=8.3 Hz), 7.34 (2H, d, J=8.5 Hz), 8.07 (2H, dd, J=2.0, 8.9 Hz), 10.98 (1H, s) FABMS (m/z): 577 [(M+Na)+]

Example 37

[0081] 2'-O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-6'-hydroxy - acetophenone (1.2 g) and p-methylthiobenzaldehyde (0.57 g) are treated in the same manner as in Example 1-(1) to give crude 2'-O-(β-D-glucopyranosyl)-6' - hydroxy-4-methylthiochalcone (1.71 g). Separately, a solution of sodium hydrogen telluride in ethanol (20 ml) is prepared from tellurium (0.3 g) and sodium borohydride (0.23 g), and thereto is added the above product, and the mixture is reacted at room temperature for one hour. The reaction mixture is poured into ice-water, and the precipitated insoluble materials are removed by filtration. To the filtrate is added chloroform, and the mixture is stirred, and the organic layer is collected. The organic layer is dried, concentrated, and the residue is purified by silica gel column chromatography to give 2'-O-(β-D-glucopyranosyl)-6'-hydroxy-4-methylthiodihydrochalcone (470 mg).

M.p. 135-136°C
IR (nujol) cm^{-1}: 3600-3200, 1620, 1600, 1230
FABMS (m/z): 473 [$(M+Na)^+$]

Example 38

[0082] Using the corresponding starting compounds, there is obtained 2'-O-(β-D-glucopyranosyl)-6'-hydroxy-3-(2-thienyl)propiophenone in the same manner as in Example 37.

M.p. 62-70°C
IR (nujol) cm^{-1}: 3600-3000, 1620, 1600, 1230
FABMS (m/z): 433 [$(M+Na)^+$]

Example 39

[0083]

(1) 6-Benzyl-2'-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl) - acetophenone (2.9 g) obtained in Example 24-(1) and 4-tetrahydropyranyl - oxybenzaldehyde (1.56 g) are dissolved in ethanol (30 ml), and thereto is added dropwise a 50 % aqueous potassium hydroxide solution (3 ml) with stirring. The mixture is treated in the same manner as in Example 1-(1), and the resulting crude product is purified by silica gel column chromatography to give 2'-O-(β-D-glucopyranosyl)-6'-benzyloxy-4-tetrahydropyranyloxychalcone (2.2. g). The above product (593 mg) and tetrabutyl ammonium hydrogen sulfate (136 mg) are added into a two-phase solvent of dichloromethane-10 % aqueous sodium hydroxide solution (10 ml/5 ml). To the mixture is added benzyl chloroformate (1.02 g), and the mixture is stirred at room temperature for one hour. The organic layer is collected, and the aqueous layer is extracted with chloroform. The combined organic layers are dried, and evaporated to remove the solvent. The resulting crude product is dissolved in a mixture of acetic acid-water-tetrahydrofuran (10 ml/3.5 ml/2 ml), and the mixture is stirred at room temperature for 40 minutes, and further stirred at 40°C for 30 minutes. The reaction solution is diluted with ethyl acetate, and washed with water, dried, and evaporated to remove the solvent. The residue is purified by silica gel column chromatography to give yellow foam (847 mg).

IR (nujol) cm^{-1}: 1760, 1750
FABMS (m/z): 1067 [$(M+Na)^+$]

(2) A mixture of the above product (816 mg), N-benzyloxycarbonyl-glycine (245 mg), dicyclohexylcarbodiimide (266 mg), 1-hydroxybenzotriazol hydrate (174 mg) and dimethylformamide (10 ml) is stirred at room temperature for 13 hours. The reaction solution is diluted with ethyl acetate, and the insoluble materials are removed by filtration. The filtrate is washed with water, dried, and evaporated to remove the solvent. The residue is purified by silica gel column chromatography to give pale yellow foam (848 mg).

IR (nujol) cm^{-1}: 3400, 1765, 1730, 1650
FABMS (m/z): 1258 [$(M+Na)^+$]

(3) The above product (811 mg) is dissolved in ethanol (10 ml), and thereto are added 10 % palladium-carbon (0.2 g) and 19 % hydrogen chloride - ethanol (0.2 ml), and the mixture is subjected to catalytic hydrogenation at room temperature. After the reaction is complete, the catalyst is removed by filtration, and the filtrate is concentrated. The residue is pulverized in diethyl ether. The resulting powders are collected by filtration, dried to give 2'-O-(β-D-glucopyranosyl)-6'-hydroxy-4-glycyloxydihydrochalcone hydrochloride (130 mg).

M.p. 72°C ~ (gradually melting)
NMR ($DMSO-d_6$) δ : 2.93 (2H, t, J=7.3 Hz), 3.12-3.53 (7H, m), 3.69 (1H, d, J=10.9 Hz), 4.07 (2H, s), 4.69 (1H, bro), 4.91 (1H, d, J=7.4 Hz), 5.10 (1H, bro), 5.19 (1H, bro), 5.29 (1H, d, J=4.1 Hz), 6.58 (1H, d, J=8.1 Hz), 6.68 (1H, d, J=8.3 Hz), 7.08 (2H, ddd, J=2.0, 2.6, 8.5 Hz), 7.24 (1H, t, J=8.3 Hz), 7.36 (2H, d, J=8.7 Hz), 8.56 (3H, bro), 10.99 (1H, s)
IR (nujol) cm^{-1}: 3300, 1770, 1630

Example 40

[0084] Using the corresponding starting compounds, there is obtained 2'-O-(β-D-glucopyranosyl)-6'-hydroxy-4-L-valyloxydihydrochalcone hydrochloride in the same manner as in Example 39.

M.p. 141°C ~ (gradually melting)
NMR (DMSO-d_6) δ : 1.08 (3H, d, J=7.0 Hz), 1.11 (3H, d, J=7.0 Hz), 2.34 (1H, m), 2.93 (2H, t, J=7.3 Hz), 3.12-3.52 (7H, m), 3.70 (1H, d, J=11.7 Hz), 4.12 (1H, d, J=4.9 Hz), 4.59 (1H, broad), 4.91 (1H, d, J=7.5 Hz), 5.08 (1H, d, J=4.8 Hz), 5.17 (1H, d, J=2.9 Hz), 5.29 (1H, d, J=5.1 Hz), 6.58 (1H, d, J=8.4 Hz), 6.68 (1H, d, J=8.3 Hz), 7.08 (2H, d, J=8.5 Hz), 7.24 (1H, t, J=8.3 Hz), 7.37 (2H, d, J=8.5 Hz), 8.74 (3H, broad), 10.99 (1H, s)
FABMS (m/z): 542 [$(M+Na)^+$]

Example 41

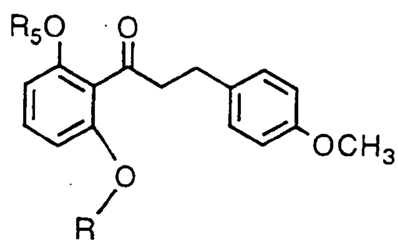
[0085] To a mixture of 4-methoxy-6'-hydroxy-2'-O-β-D-glucopyranosyl-dihydrochalcone (869 mg), potassium carbonate (830 mg) and dimethyl-formamide (10 ml) is added dropwise methyl iodide (426 mg), and the mixture is stirred at room temperature overnight. The mixture is concentrated under reduced pressure, and to the residue are added ethyl acetate and water, and stirred. The organic layer is collected, washed with water, dried, and evaporated to remove the solvent. The residue is purified by silica gel column chromatography (solvent; chloroform/methanol) to give 4,6'-dimethoxy-2'-O-β-D-glucopyranosyldihydrochalcone (0.8 g).

NMR (DMSO-d_6) δ : 2.80 (2H, t, J=8.1 Hz), 2.9-3.3 (7H, m), 3.44 (1H, dd, J=6.1, 11.9 Hz), 3.71 (6H, s), 4.55 (1H, t, J=5.9 Hz), 4.87 (1H, d, J=7.7 Hz), 5.02 (1H, d, J=5.3 Hz), 5.08 (1H, d, J=4.9 Hz), 5.19 (1H, d, J=5.5 Hz), 6.73 (1H, d, J=8.3 Hz), 6.82 (3H, d, J=8.7 Hz), 7.15 (2H, d, J=8.7 Hz), 7.30 (1H, t, J=8.4 Hz)
FABMS (m/z): 471 [$(M+Na)^+$]

Examples 42-43

[0086] Using the corresponding starting compounds, the compounds listed in Table 6 are obtained in the same manner as in Example 41.

Table 6



(R: β-D-glucopyranosyl group)

Ex. No.	R^5O	Physical properties
52	$CH_3(CH_2)_3O$-	M.p. 104-107°C IR (nujol) cm^{-1}: 3340 (broad), 1690 FABMS (m/z): 513 [$(M+Na)^+$]
53	$(CH_3)_2CHO$-	IR (nujol) cm^{-1}: 3340 (broad), 1700 FABMS (m/z): 499 [$(M+Na)^+$]

Example 44

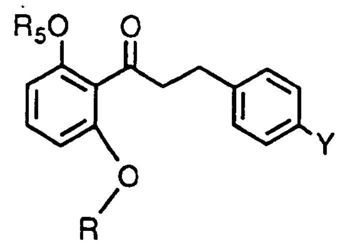
[0087] 4-Methoxy-6'-hydroxy-2'-O-β-D-glucopyranosyldihydrochalcone (868 mg) is dissolved in dimethylacetoamide (10 ml), and thereto is added triethylamine (212 mg), and then thereto is added ethyl chlorocarbonate (228 mg) under ice-cooling. The mixture is stirred at the same temperature for 40 minutes, and thereto is added ethyl acetate. The mixture is stirred and the organic layer is collected, washed with water, dried and evaporated to remove the solvent. The residue is purified by silica gel column chromatography (solvent; chloroform/methanol) to give 4-methoxy-6'-ethoxycarbonyl-2'-O-β-D-glucopyranosyldihydrochalcone (534 mg).

NMR ($DMSO-d_6$) δ : 1.26 (3H, t, J=7.1 Hz), 2.80 (2H, m), 3.0-3.5 (7H, m), 3.70 (1H, m), 3.71 (3H, s), 4.18 (2H, q, J=7.1 Hz), 4.57 (1H, t, J=5.7 Hz), 5.02 (1H, d, J=7.4 Hz), 5.05 (1H, d, J=5.3 Hz), 5.11 (1H, d, J=4.8 Hz), 5.31 (1H, d, J=5.5 Hz), 6.82 (2H, ddd, J=2.1, 3.0, 8.7 Hz), 6.95 (1H, d, J=8.4 Hz), 7.15 (2H, ddd, J=2.0, 2.9, 8.6 Hz), 7.18 (1H, t, J=7.9 Hz), 7.44 (1H, t, J=8.3 Hz) FABMS (m/z): 529 [$(M+Na)^+$]

Examples 45-50

[0088] Using the corresponding starting compounds, the compounds listed in Table 7 are obtained in the same manner as in Examples 44.

Table 7



(R: β-D-glucopyranosyl group)

Ex. No.	Y	R^5O	Physical properties
45	CH_3O-	$(CH_3)_2CH$-CH_2OCOO-	NMR (DMSO-d_6) δ : 0.91 (6H, d, J=6.8 Hz), 1.94 (1H, m), 2.80 (2H, m), 3.0-3.5 (7H, m), 3.70 (1H, m), 3.71 (3H, s), 3.94 (2H, d, J=6.6 Hz), 4.57 (1H, t, J=5.8 Hz), 5.02 (1H, d, J=7.6 Hz), 5.05 (1H, d, J=5.3 Hz), 5.11 (1H, d, J=4.8 Hz), 5.31 (1H, d, J=5.5 Hz), 6.82 (2H, ddd, J=2.1, 3.0, 8.7 Hz), 6.95 (1H, d, J=8.4 Hz), 7.15 (2H, dd, J=2.0, 8.7 Hz), 7.18 (1H, d, J=8.3 Hz), 7.44 (1H, t, J=8.3 Hz) FABMS (m/z): 557 [$(M+Na)^+$]
46	CH_3COO-	CH_3COO-	NMR (DMSO-d_6) δ : 2.05 (3H, s), 2.24 (3H, s), 2.87 (2H, m), 3.0-3.5 (7H, m), 3.70 (1H, ddd, J=1.6, 5.3, 11.5 Hz), 4.57 (1H, t, J=5.8 Hz), 5.00 (1H, d, J=7.4 Hz), 5.04 (1H, d, J=5.3 Hz), 5.10 (1H, d, J=4.8 Hz), 5.35 (1H, d, J=5.5 Hz), 6.83 (1H, d, J=7.7 Hz), 7.01 (2H, ddd, J=2.0, 2.7, 8.5 Hz), 7.15 (1H, d, J=8.4 Hz), 7.28 (2H, ddd, J=2.0, 2.7, 8.5 Hz), 7.41 (1H, t, J=8.3 Hz) FABMS (m/z): 527 [$(M+Na)^+$]

47	$(CH_3)_2CH$ - COO-	$(CH_3)_2CH$ - COO-	NMR (DMSO-d_6) δ : 1.12 (6H, d, J=7.0 Hz), 1.22 (6H, d, J=7.0 Hz), 2.62 (1H, m), 2.79 (1H, m), 2.86 (2H, t, J=7.7 Hz), 3.0-3.5 (7H, m), 3.70 (1H, ddd, J=1.7, 5.4, 11.7 Hz), 4.58 (1H, t, J=5.7 Hz), 5.01 (1H, d, J=7.5 Hz), 5.04 (1H, d, J=5.2 Hz), 5.10 (1H, d, J=4.8 Hz), 5.35 (1H, d, J=5.5 Hz), 6.82 (1H, dd, J=0.7, 8.1 Hz), 6.99 (2H, dd, J=2.0, 8.6 Hz), 7.15 (1H, d, J=8.1 Hz), 7.27 (2H, dd, J=1.9, 8.5 Hz), 7.42 (1H, t, J=8.3 Hz) FABMS (m/z): 583 [$(M+Na)^+$]
48	$(CH_3)_2CH$ - CH_2OCOO-	$(CH_3)_3C$ - COO-	NMR (DMSO-d_6) δ : 0.94 (6H, d, J=6.8 Hz), 1.18 (9H, s), 1.97 (1H, m), 2.86 (2H, t, J=7.6 Hz), 3.0-3.5 (7H, m), 3.71 (1H, m), 3.99 (2H, d, J=6.6 Hz), 4.58 (1H, t, J=5.8 Hz), 5.00 (1H, d, J=7.4 Hz), 5.04 (1H, d, J=5.3 Hz), 5.10 (1H, d, J=4.8 Hz), 5.35 (1H, d, J=5.5 Hz), 6.81 (1H, d, J=8.1 Hz), 7.11 (2H, dd, J=2.7, 8.5 Hz), 7.16 (1H, d, J=8.6 Hz), 7.28 (2H, d, J=8.6 Hz), 7.42 (1H, t, J=8.3 Hz) FABMS (m/z): 637 [$(M+Na)^+$]
49	CH_3CH_2O - COO-	CH_3CH_2O - COO-	NMR (DMSO-d_6) δ : 1.25 (3H, t, J=7.1 Hz), 1.28 (3H, t, J=7.1 Hz), 2.88 (2H, m), 3.1-3.3 (5H, m), 3.37 (1H, m), 3.46 (1H, m), 3.70 (1H, ddd, J=1.5, 5.1, 11.3 Hz), 4.19 (2H, q, J=7.1 Hz), 4.23 (2H, q, J=7.1 Hz), 4.58 (1H, t, J=5.8 Hz), 5.02 (1H, d, J=7.5 Hz), 5.05 (1H, d, J=5.3 Hz), 5.12 (1H, d, J=5.0 Hz), 5.36 (1H, d, J=5.5 Hz), 6.96 (1H, d, J=7.4 Hz), 7.11 (2H, ddd, J=2.0, 2.8, 8.6 Hz), 7.19 (1H, d, J=8.1 Hz), 7.30 (2H, dd, J=2.0, 8.7 Hz), 7.45 (1H, t, J=8.3 Hz) FABMS (m/z): 587 [$(M+Na)^+$]

50	$(CH_3)_2CH$ - CH_2OCOO-	$(CH_3)_2CH$ - CH_2OCOO-	NMR (DMSO-d_6) δ : 0.91 (6H, d, J=6.7 Hz), 0.93 (6H, d, J=6.8 Hz), 1.96 (2H, m), 2.87 (2H, t, J=7.4 Hz), 3.1-3.3 (5H, m), 3.37 (1H, m), 3.47 (1H, m), 3.70 (1H, ddd, J=1.6, 5.2, 11.4 Hz), 3.95 (2H, d, J=6.6 Hz), 3.99 (2H, d, J=6.6 Hz), 4.58 (1H, t, J=5.7 Hz), 5.02 (1H, d, J=7.4 Hz), 5.05 (1H, d, J=5.3 Hz), 5.11 (1H, d, J=4.9 Hz), 5.36 (1H, d, J=5.5 Hz), 6.96 (1H, d, J=7.4 Hz), 7.11 (2H, ddd, J=2.1, 2.7, 8.6 Hz), 7.19 (1H, d, J=8.0 Hz), 7.29 (2H, ddd, J=1.9, 2.7, 8.6 Hz), 7.45 (1H, t, J=8.3 Hz) FABMS (m/z): 643 [$(M+Na)^+$]

Example 51

[0089]

(1) To a mixture of ethanol-methanol (1:1) (80 ml) are added 2'-O - [2,3,6-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-β-D - glucopyranosyl]-6'-hydroxyacetophenone (4.3 g) and p-anisaldehyde (1.52 g), and thereto is added dropwise a 50 % aqueous potassium hydroxide solution (6 ml) with stirring. The mixture is treated in the same manner as in Example 1 - (1), and the resulting crude product is purified by silica gel column chromatography to give 2'-O-[4-O-(α-D-glucopyranosyl)-β-D-glucopyranosyl]-6' - hydroxy-4-methoxychalcone (1.71 g).

IR (nujol) cm^{-1}: 3600-2400, 1620
FABMS (m/z): 595 [$(M+Na)^+$], 271

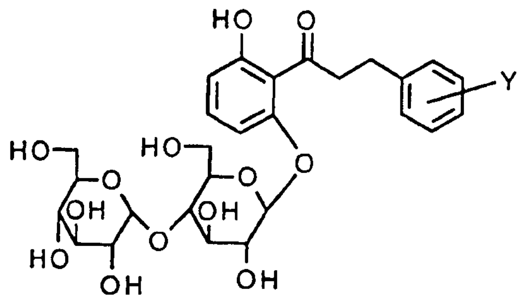
(2) 2'-O-[4-O-(α-D-Glucopyranosyl)-β-D-glucopyranosyl]-6'-hydroxy - 4-methoxychalcone (1.64 g) is dissolved in tetrahydrofuran (30 ml), and the mixture is treated in the same manner as in Example 1-(2) to give 2'-O-[4-O-(α - D-glucopyranosyl)-β-D-glucopyranosyl]-6'-hydroxy-4-methoxydihydrochalcone (931 mg).

M.p. 92°C ~ (gradually melting)
NMR (DMSO-d_6) δ : 2.83 (2H, t, J=7.3 Hz), 3.22 (2H, t, J=7.3 Hz), 3.0-3.8 (12H, m), 3.71 (3H, s), 4.55 (2H, m), 4.90 (1H, d, J=4.4 Hz), 4.92 (1H, d, J=5.4 Hz), 4.97 (1H, d, J=7.8 Hz), 5.06 (1H, d, J=3.9 Hz), 5.37 (1H, d, J=5.9 Hz), 5.48 (1H, d, J=5.9 Hz), 5.62 (1H, d, J=2.9 Hz), 6.55 (1H, d, J=7.8 Hz), 6.68 (1H, d, J=8.3 Hz), 6.82 (2H, dd, J=2.9, 8.8 Hz), 7.17 (2H, dd, J=2.9, 8.3 Hz), 7.24 (1H, t, J=8.3 Hz), 10.95 (1H, brs)
IR (nujol) cm^{-1}: 3340, 1620
FABMS (m/z): 597 (NH^+)

Examples 52-55

[0090] Using the corresponding starting compounds, the compounds listed in Table 8 are obtained in the same manner as in Example 51.

Table 8



Ex. No.	Y	Physical properties
52	4-HO-	M.p. 165°C ~ (gradually melting) NMR (DMSO-d_6) δ : 2.78 (2H, t, J=7.3 Hz), 3.0-3.8 (14H, m), 4.55 (2H, m), 4.90 (1H, d, J=4.4 Hz), 4.93 (1H, d, J=5.0 Hz), 4.97 (1H, d, J=7.8 Hz), 5.06 (1H, d, J=3.4 Hz), 5.37 (1H, d, J=5.9 Hz), 5.49 (1H, d, J=5.9 Hz), 5.62 (1H, d, J=2.9 Hz), 6.55 (1H, d, J=8.3 Hz), 6.64 (2H, d, J=8.3 Hz), 6.67 (1H, d, J=8.3 Hz), 7.03 (2H, d, J=8.3 Hz), 7.24 (1H, t, J=8.3 Hz), 9.10 (1H, brs), 10.97 (1H, brs) IR (nujol) cm^{-1}: 3320, 1630 FABMS (m/z): 583 (NH^+)
53	H-	M.p. 89°C ~ (gradually melting) NMR (DMSO-d_6) δ : 2.90 (2H, t, J=7.3 Hz), 3.03 - 3.78 (14H, m), 4.51 (1H, t, J=5.5 Hz), 4.56 (1H, t, J=5.7 Hz), 4.89 (1H, d, J=4.9 Hz), 4.91 (1H, d, J=5.6 Hz), 4.98 (1H, d, J=7.9 Hz), 5.06 (1H, d, J=3.7 Hz), 5.37 (1H, d, J=5.8 Hz), 5.47 (1H, d, J=6.1 Hz), 5.61 (1H, d, J=3.3 Hz), 6.56 (1H, d, J=8.3 Hz), 6.68 (1H, d, J=8.1 Hz), 7.17 (1H, m), 7.24 (1H, t, J=8.3 Hz), 7.26 (4H, m), 10.93 (1H, s) FABMS (m/z): 589 [(M+Na)+]
54	4-Cl-	M.p. 91°C ~ (gradually melting) NMR (DMSO-d_6) δ : 2.90 (2H, t, J=7.3 Hz), 3.03 - 3.77 (14H, m), 4.52 (1H, t, J=5.5 Hz), 4.57 (1H, t, J=5.7 Hz), 4.89 (1H, d, J=4.9 Hz), 4.92 (1H, d, J=5.6 Hz), 4.98 (1H, d, J=7.8 Hz), 5.06 (1H, d, J=3.9 Hz), 5.39 (1H, d, J=5.7 Hz), 5.48 (1H, d, J=6.1 Hz), 5.62 (1H, d, J=3.3 Hz), 6.55 (1H, d, J=8.4 Hz), 6.68 (1H, d, J=8.5 Hz), 7.24 (1H, t, J=8.3 Hz), 7.30 (4H, s), 10.91 (1H, s) FABMS (m/z): 623, 625 [(M+Na)+]

55	3-CH_3-	M.p. 92°C ~ (gradually melting) NMR (DMSO-d_6) δ : 2.27 (3H, s), 2.86 (2H, t, J=7.5 Hz), 3.03-3.78 (14H, m), 4.51 (1H, t, J=5.5 Hz), 4.56 (1H, t, J=5.7 Hz), 4.89 (1H, d, J=4.9 Hz), 4.91 (1H, d, J=5.6 Hz), 4.98 (1H, d, J=7.7 Hz), 5.05 (1H, d, J=3.7 Hz), 5.36 (1H, d, J=5.8 Hz), 5.48 (1H, d, J=6.1 Hz), 5.61 (1H, d, J=3.2 Hz), 6.56 (1H, d, J=8.1 Hz), 6.68 (1H, d, J=8.4 Hz), 6.97 (1H, d, J=7.3 Hz), 7.04 (1H, d, J=7.7 Hz), 7.07 (1H, s), 7.14 (1H, t, J=7.4 Hz), 7.25 (1H, t, J=8.3 Hz), 10.95 (1H, s) FABMS (m/z): 603 [(M+Na)+]

Example 56 (Reference)

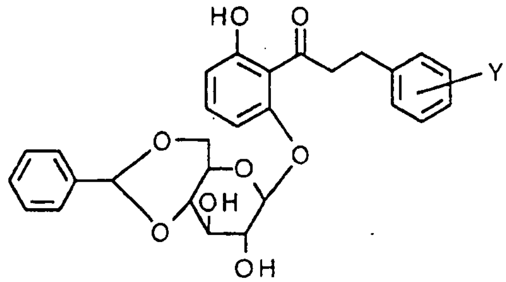
[0091] To a mixture of dioxane-methylene chloride (20 ml/100 ml) is added 4-methoxy-6'-hydroxy-2'-O-β-D-glucopyranosyldihydrochalcone (2.79 g), and thereto are added benzaldehydedimethylacetal (1.47 g) and p-toluenesulfonic acid (120 mg) with stirring, and the mixture is stirred at room temperature for 20 hours. The reaction solution is washed with water, dried, and filtered, and the filtrate is concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform/methanol) to give 4 - methoxy-6'-hydroxy-2'-O-(4,6-O-benzylidene-β-D-glucopyranosyl)dihydro - chalcone (2.65 g) as white powders.

M.p. 126-130°C
FABMS (m/s): 545 [(M+Na)+]
NMR (DMSO-d_6) δ : 2.84 (2H, t, J=7.6 Hz), 3.19 (2H, t, J=7.6 Hz), 3.3-3.7 (5H, m), 3.72 (3H, s), 4.21 (1H, d, J=4.9 Hz), 5.16 (1H, d, J=7.8 Hz), 5.48 (1H, d, J=5.4 Hz), 5.59 (1H, d, J=5.4 Hz), 5.60 (1H, s), 6.57 (1H, d, J=7.8 Hz), 6.72 (1H, d, J=8.3 Hz), 6.84 (2H, ddd, J=2.0, 2.9, 8.8 Hz), 7.17 (2H, ddd, J=2.0, 2.7, 8.3 Hz), 7.25 (1H, t, J=8.3 Hz), 7.40 (5H, m), 10.85 (1H, s)

Examples 57-62 (Reference)

[0092] Using the corresponding starting compounds, the compounds listed in Table 9 are obtained in the same manner as in Example 56.

Table 9



Ex. No.	Y	Physical properties
57	H-	M.p. 135-136°C FABMS (m/z): 515 [(M+Na)+] NMR (DMSO-d6) δ : 2.91 (2H, t, J=7.4 Hz), 3.23 (2H, t, J=7.4 Hz), 3.3-3.7 (5H, m), 4.21 (1H, dd, J=3.2, 8.5 Hz), 5.17 (1H, d, J=7.7 Hz), 5.48 (1H, d, J=5.2 Hz), 5.59 (1H, d, J=5.8 Hz), 5.60 (1H, s), 6.58 (1H, d, J=8.2 Hz), 6.72 (1H, d, J=8.5 Hz), 7.1-7.3 (5H, m), 7.25 (1H, t, J=8.3 Hz), 7.3-7.5 (5H, m), 10.83 (1H, s)
58	4-OH-	FABMS (m/z): 531 [(M+Na)+] NMR (DMSO-d6) δ : 2.78 (2H, t, J=7.3 Hz), 3.16 (2H, t, J=7.6 Hz), 3.3-3.7 (5H, m), 4.20 (1H, d, J=4.9 Hz), 5.16 (1H, d, J=7.8 Hz), 5.48 (1H, d, J=4.9 Hz), 5.58 (1H, d, J=4.9 Hz), 5.60 (1H, s), 6.57 (1H, d, J=7.8 Hz), 6.67 (2H, d, J=8.3 Hz), 6.71 (1H, d, J=8.3 Hz), 7.04 (2H, d, J=8.3 Hz), 7.25 (1H, t, J=8.3 Hz), 7.36-7.49 (5H, m), 9.12 (1H, s), 10.87 (1H, s)
59	4-CH_3-	FABMS (m/z): 529 [(M+Na)+] NMR (DMSO-d6) δ : 2.26 (3H, s), 2.86 (2H, t, J=7.6 Hz), 3.21 (2H, t, J=7.3 Hz), 3.3-3.7 (5H, m), 4.21 (1H, d, J=4.9 Hz), 5.16 (1H, d, J=7.8 Hz), 5.48 (1H, d, J=4.9 Hz), 5.58 (1H, d, J=5.9 Hz), 5.60 (1H, s), 6.57 (1H, d, J=8.3 Hz), 6.72 (1H, d, J=7.8 Hz), 7.11 (4H, m), 7.25 (1H, t, J=8.3 Hz), 7.36-7.49 (5H, m), 10.86 (1H, s)
60	3-CH_3-	FABMS (m/z): 529 [(M+Na)+] NMR (DMSO-d6) δ : 2.28 (3H, s), 2.87 (2H, t, J=7.4 Hz), 3.22 (2H, t, J=7.4 Hz), 3.3-3.7 (5H, m), 4.21 (1H, dd, J=3.1, 8.3 Hz), 5.17 (1H, d, J=7.8 Hz), 5.48 (1H, d, J=5.2 Hz), 5.58 (1H, d, J=5.7 Hz), 5.59 (1H, s), 6.58 (1H, d, J=8.2 Hz), 6.72 (1H, d, J=8.5 Hz), 7.0-7.1 (3H, m), 7.17 (1H, t, J=7.4 Hz), 7.25 (1H, t, J=8.3 Hz), 7.3 - 7.5 (5H, m), 10.83 (1H, s)

61	4-Cl-	FABMS (m/z): 549/551 [(M+Na)+] NMR (DMSO-d_6) δ : 2.90 (2H, t, J=7.3 Hz), 3.23 (2H, m), 3.30-3.72 (5H, m), 4.21 (1H, m), 5.16 (1H, d, J=7.7 Hz), 5.49 (1H, d, J=5.3 Hz), 5.60 (1H, s), 5.61 (1H, d, J=5.6 Hz), 6.57 (1H, d, J=8.3 Hz), 6.72 (1H, d, J=8.5 Hz), 7.21-7.48 (10H, m), 10.82 (1H, s)
62	4-CH_3CH_2 - OCOO-	FABMS (m/z): 603 [(M+Na)+] NMR (DMSO-d_6) δ : 1.28 (3H, t, J=7.1 Hz), 2.92 (2H, t, J=7.4 Hz), 3.24 (2H, t, J=7.3 Hz), 3.28-3.73 (5H, m), 4.21 (1H, m), 4.23 (2H, q, J=7.1 Hz), 5.17 (1H, d, J=7.9 Hz), 5.47 (1H, d, J=5.3 Hz), 5.60 (1H, s), 5.61 (1H, d, J=5.4 Hz), 6.57 (1H, d, J=8.2 Hz), 6.72 (1H, d, J=8.5 Hz), 7.13 (2H, ddd, J=2.0, 2.8, 8.5 Hz), 7.25 (1H, t, J=8.3 Hz), 7.31 (2H, ddd, J=1.9, 2.6, 8.7 Hz), 7.35-7.48 (5H, m), 10.83 (1H, s)

Example 63

[0093]

(1) 4-Methoxy-6'-hydroxy-2'-O-(4,6-O-benzylidene-β-D-glucopyranosyl)dihydrochalcone (1.86 g) is dissolved in pyridine (40 ml), and thereto is added acetic anhydride (10 ml). The mixture is reacted at room temperature for three hours, and concentrated under reduced pressure. To the residue is added isopropyl ether, and the precipitated powders are collected by filtration, washed, and dried to give 4-methoxy-6'-acetoxy-2'-O-(2,3-di-O-acetyl-4,6-O-benzylidene-β-D-glucopyranosyl)dihydrochalcone (2.06 g) as white powders.

M.p. 175.5-176.5°C
FABMS (m/z): 649 (MH^+)

(2) To a 80 % aqueous acetic acid solution (30 ml) is added the above obtained 4-methoxy-6'-acetoxy-2'-O-(2,3-di-O-acetyl-4,6-O-benzylidene-β-D-glucopyranosyl)dihydrochalcone (1.00 g), and the mixture is heated with stirring at 70°C for two hours. The reaction solution is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (solvent; chloroform/methanol) to give 4-methoxy-6'-acetoxy-2'-O-(2,3-di-O-acetyl-β-D-glucopyranosyl)dihydrochalcone (820 mg) as white amorphous powders.

FABMS (m/z): 583 [$(M+Na)^+$]
NMR (DMSO-d_6) δ : 1.89 (3H, s), 2.00 (3H, s), 2.06 (3H, s), 2.77 (2H, m), 2.88 (2H, m), 3.4-3.8 (4H, m), 3.71 (3H, s), 4.76 (1H, t, J=5.9 Hz), 4.88 (1H, dd, J=7.8, 9.8 Hz), 5.11 (1H, dd, J=9.3, 9.8 Hz), 5.50 (1H, d, J=7.8 Hz), 5.59 (1H, d, J=5.9 Hz), 6.84 (2H, ddd, J=2.0, 2.9, 8.3 Hz), 6.88 (1H, d, J=8.3 Hz), 7.13 (2H, ddd, J=2.0, 2.9, 8.3 Hz), 7.15 (1H, d, J=7.8 Hz), 7.44 (1H, t, J=8.3 Hz)

Example 64

[0094]

(1) To a mixture of methanol-tetrahydrofuran (30 ml/100 ml) are added 4-methoxy-6'-acetoxy-2'-O-(2,3-di-O-acetyl-4,6-O-benzylidene-β-D - glucopyranosyl)dihydrochalcone (1.05 g) and sodium hydrogen carbonate (272 mg), and the mixture is stirred at room temperature for four hours, and then stirred at 40°C for 30 minutes. The mixture is

concentrated under reduced pressure, and to the residue are added ethyl acetate and water. The mixture is stirred and the organic layer is collected, washed with water, and dried. The mixture is filtered, and the filtrate is concentrated. To the residue is added isopropyl ether, and the precipitated white powders are collected by filtration, washed, and dried to give 4-methoxy-6'-hydroxy-2'-O-(2,3-di-O-acetyl-4,6-O - benzylidene-β-D-glucopyranosyl)dihydrochalcone (911 mg).

M.p. 149-151°C
FABMS (m/z): 607 (MH^+)

(2) The above obtained 4-methoxy-6'-hydroxy-2'-O-(2,3-di-O-acetyl - 4,6-O-benzylidene-β-D-glucopyranosyl)dihydrochalcone (900 mg) is treated in the same manner as in Example 63-(2) to give 4-methoxy-6'-hydroxy-2'-O-(2,3 - di-O-acetyl-β-D-glucopyranosyl)dihydrochalcone (640 mg) as white powders.

M.p. 136-138°C
FABMS (m/z): 541 [$(M+Na)^+$]
NMR (DMSO-d_6) δ : 1.93 (3H, s), 2.00 (3H, s), 2.76 (2H, m), 2.90 (2H, m), 3.4-3.8 (4H, m), 3.71 (3H, s), 4.73 (1H, t, J=5.6 Hz), 4.85 (1H, dd, J=7.8, 9.8 Hz), 5.09 (1H, dd, J=8.8, 9.8 Hz), 5.35 (1H, d, J=7.8 Hz), 5.56 (1H, d, J=5.4 Hz), 6.57 (1H, d, J=7.8 Hz), 6.67 (1H, d, J=8.3 Hz), 6.83 (2H, ddd, J=2.0, 2.9, 8.8 Hz), 7.13 (2H, ddd, J=2.4, 2.9, 8.8 Hz), 7.19 (1H, t, J=8.3 Hz), 10.26 (1H, s)

Example 65

[0095]

(1) 4-Methoxy-6'-hydroxy-2'-O-(4,6-O-benzylidene-β-D-glucopyranosyl)dihydrochalcone (1.045 g) is dissolved in pyridine (20 ml), and thereto is added dropwise with stirring n-butyryl chloride (1.28 g) under ice - cooling. The mixture is reacted at room temperature for two hours, and concentrated under reduced pressure. To the residue are added ethyl acetate and ice-cold diluted hydrochloric acid. The mixture is stirred and the organic layer is collected, washed with water, filtered, and concentrated. To the residue are added methanol (20 ml) and sodium hydrogen carbonate (0.84 g), and the mixture is stirred at 40°C for four hours. The mixture is concentrated, and to the residue are added ethyl acetate and water. The mixture is stirred and the organic layer is collected, dried, filtered, and concentrated. The residue is purified by silica gel column chromatography (solvent; ethyl acetate/n-hexane) to give 4-methoxy-6'-hydroxy-2'-O-(2,3-di-O-butyryl-4,6-O-benzylidene-β-D-glucopyranosyl)dihydrochalcone (0.80 g) as white powders.

FABMS (m/z): 662 (MH^+)

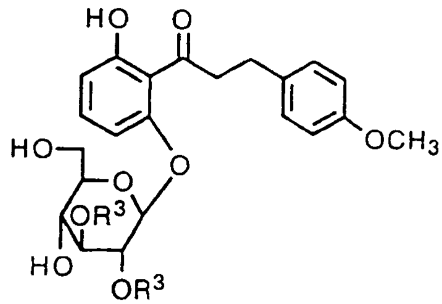
(2) The above obtained 4-methoxy-6'-hydroxy-2'-O-(2,3-di-O-butyryl-4,6-O-benzylidene-β-D-glucopyranosyl)dihydrochalcone (0.75 g) is added to a 80 % aqueous acetic acid solution (50 ml), and the mixture is heated at 70°C for two hours. The mixture is treated in the same manner as in Example 8-(2) to give 4-methoxy-6'-hydroxy-2'-O-(2,3-di-O-butyryl-β-D-glucopyranosyl)dihydrochalcone (0.54 g) as white powders.

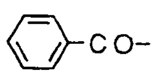
M.p. 126-127°C
FABMS (m/z): 597 [$(M+Na)]^+$
NMR (DMSO-d_6) δ : 0.79 (3H, t, J=7.3 Hz), 0.87 (3H, t, J=7.3 Hz), 1.3-1.6 (4H, m), 2.1-2.3 (4H, m), 2.7-2.9 (4H, m), 3.5-3.7 (4H, m), 3.71 (3H, s), 4.73 (1H, t, J=5.9 Hz), 4.89 (1H, t, J=7.8 Hz), 5.12 (1H, d, J=8.8 Hz), 5.38 (1H, d, J=7.8 Hz), 5.53 (1H, d, J=5.9 Hz), 6.56 (1H, d, J=8.3 Hz), 6.67 (1H, d, J=8.3 Hz), 6.83 (2H, d, J=8.3 Hz), 7.13 (2H, d, J=8.3 Hz), 7.18 (1H, t, J=8.3 Hz), 10.26 (1H, s)

Examples 66-99

[0096] Using the corresponding starting compounds, the compounds listed in Tables 10-16 are obtained in the same manner as in Examples 63, 64 and 65.

Table 10

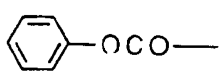


Ex. No.	R^3	Physical properties
66	$(CH_3)_2CHCO$-	FABMS (m/z): 597 [(M+Na)+] NMR (DMSO-d_6) δ : 0.9-1.1 (12H, m), 2.3-2.5 (2H, m), 2.8-3.0 (4H, m), 3.5-3.8 (4H, m), 3.71 (3H, s), 4.72 (1H, t, J=8.0 Hz), 4.89 (1H, t, J=7.8 Hz), 5.13 (1H, t, J=8.8 Hz), 5.42 (1H, d, J=7.8 Hz), 5.53 (1H, d, J=5.9 Hz), 6.56 (1H, d, J=5.9 Hz), 6.67 (1H, d, J=8.3 Hz), 6.83 (2H, d, J=8.8 Hz), 7.1-7.2 (3H, m), 10.26 (1H, s)
67		FABMS (m/z): 665 [(M+Na)+] NMR (DMSO-d_6) δ : 2.5-3.0 (4H, m), 3.60 (1H, m), 3.70 (3H, s), 3.78 (3H, m), 4.80 (1H, broad), 5.31 (1H, dd, J=7.8, 9.8 Hz), 5.58 (1H, m), 5.70 (1H, d, J=7.8 Hz), 5.72 (1H, broad), 6.54 (1H, d, J=8.3 Hz), 6.74 (1H, d, J=8.8 Hz), 6.75 (2H, d, J=8.8 Hz), 6.95 (2H, d, J=8.8 Hz), 7.20 (1H, t, J=8.3 Hz), 7.40 (4H, m), 7.58 (2H, m), 7.77 (2H, dd, J=1.5, 8.8 Hz), 7.87 (2H, dd, J=1.5, 8.3 Hz), 10.26 (1H, s)

68	CH_3OCH_2CO-	M.p. 98-100°C FABMS (m/z): 601 [(M+Na)+] NMR (DMSO-d_6) δ : 2.76 (2H,m), 2.93 (2H, m), 3.26 (3H, s), 3.29 (3H, s), 3.4-3.8 (4H, m), 3.71 (3H, s), 3.92 (2H, dd, J=8.8, 17.1 Hz), 4.08 (2H, dd, J=7.8, 16.6 Hz), 4.75 (1H, t, J=5.6 Hz), 4.93 (1H, dd, J=7.8, 9.8 Hz), 5.19 (1H, t, J=9.8 Hz), 5.43 (1H, d, J=8.3 Hz), 5.64 (1H, d, J=5.4 Hz), 6.57 (1H, d, J=8.3 Hz), 6.68 (1H, d, J=8.3 Hz), 6.82 (2H, ddd, J=2.0, 2.9, 8.8 Hz), 7.13 (2H, ddd, J=2.0, 2.9, 8.3 Hz), 7.19 (1H, t, J=8.3 Hz), 10.27 (1H, s)
69	$CH_3CH_2OCH_2CO$-	M.p. 96-99°C FABMS (m/z): 629 [(M+Na)+] NMR (DMSO-d_6) δ : 1.07 (3H, t, J=6.8 Hz), 1.12 (3H, t, J=6.8 Hz), 2.76 (2H, m), 2.88 (2H, m), 3.44 (4H, m), 3.4-3.8 (4H, m), 3.71 (3H, s), 3.95 (2H, dd, J=9.3, 16.6 Hz), 4.10 (2H, dd, J=8.1, 16.8 Hz), 4.75 (1H, t, J=5.4 Hz), 4.91 (1H, dd, J=7.8, 9.8 Hz), 5.18 (1H, dd, J=8.8, 9.8 Hz), 5.42 (1H, d, J=7.8 Hz), 5.63 (1H, d, J=5.4 Hz), 6.57 (1H, d, J=8.3 Hz), 6.68 (1H, d, J=8.3 Hz), 6.82 (2H, ddd, J=2.0, 2.9, 8.3 Hz), 7.13 (2H, ddd, J=1.5, 2.9, 8.3 Hz), 7.19 (1H, t, J=8.3 Hz), 10.27 (1H, s)
70	$CH_3(CH_2)_2OCH_2CO$-	M.p. 96-99°C FABMS (m/z): 657 [(M+Na)+] NMR (DMSO-d_6) δ : 0.8-0.9 (6H, m), 1.4-1.5 (4H, m), 2.7-2.9 (4H, m), 3.3-3.4 (4H, m), 3.5 - 3.8 (4H, m), 3.71 (3H, s), 3.95 (2H, dd, J=10.3, 16.6 Hz), 4.10 (2H, dd, J=8.3. 16.6 Hz), 4.75 (1H, t, J=5.9 Hz), 4.92 (1H, dd, J=7.8, 9.8 Hz), 5.17 (1H, t, J=9.8 Hz), 5.41 (1H, d, J=7.8 Hz), 5.63 (1H, d, J=5.4 Hz), 6.57 (1H, d, J=8.3 Hz), 6.68 (1H, d, J=8.3 Hz), 6.82 (2H, d, J=8.3 Hz), 7.13 (2H, d, J=8.8 Hz), 7.19 (1H, t, J=8.3 Hz), 10.28 (1H, s)

71	$(CH_3)_2CHOCH_2CO$-	FABMS (m/z): 657 [(M+Na)+] NMR (DMSO-d_6) δ : 1.0-1.1 (12H, m), 2.7-2.9 (4H, m), 3.4-3.8 (6H, m), 3.71 (3H, s), 3.93 (2H, dd, J=11.2, 17.1 Hz), 4.10 (2H, dd, J=6.3, 16.9 Hz), 4.75 (1H, t, J=5.4 Hz), 4.91 (1H, dd, J=7.8, 9.8 Hz), 5.17 (1H, t, J=8.8 Hz), 5.40 (1H, d, J=7.8 Hz), 5.62 (1H, d, J=5.4 Hz), 6.57 (1H, d, J=8.3 Hz), 6.68 (1H, d, J=7.8 Hz), 6.82 (2H, d, J=8.8 Hz), 7.13 (2H, d, J=8.8 Hz), 7.19 (1H, t, J=8.3 Hz), 10.28 (1H, s)
72	$(CH_3)_2CHCH_2OCH_2CO$-	FABMS (m/z): 685 [(M+Na)+] NMR (DMSO-d_6) δ : 0.81 (6H, d, J=6.8 Hz), 0.87 (6H, d, J=6.9 Hz), 1.7-1.8 (2H, m), 2.7 - 2.9 (4H, m), 3.1-3.3 (4H, m), 3.5-3.7 (4H, m), 3.71 (3H, s), 3.96 (2H, dd, J=10.8, 16.9 Hz), 4.11 (2H, dd, J=7.3, 16.6 Hz), 4.75 (1H, t, J=5.9 Hz), 4.92 (1H, dd, J=7.8, 9.8 Hz), 5.17 (1H, t, J=9.8 Hz), 5.40 (1H, d, J=7.8 Hz), 5.63 (1H, d, J=5.4 Hz), 6.57 (1H, d, J=7.8 Hz), 6.68 (1H, d, J=8.3 Hz), 6.82 (2H, d, J=8.3 Hz), 7.13 (2H, d, J=8.3 Hz), 7.19 (1H, t, J=8.3 Hz), 10.23 (1H, s)
73	$CH_3O(CH_2)_2OCH_2CO$-	M.p. 104-105°C FABMS (m/z): 689 [(M+Na)+] NMR (DMSO-d_6) δ : 2.7-2.8 (2H, m), 2.9-3.0 (2H, m), 3.21 (3H, s), 3.25 (3H, s), 3.3-3.7 (12H, m), 3.71 (3H, s), 4.01 (2H, dd, J=8.8, 17.1 Hz), 4.15 (2H, dd, J=7.3, 17.1 Hz), 4.75 (1H, t, J=5.9 Hz), 4.91 (1H, dd, J=7.8, 9.8 Hz), 5.17 (1H, t, J=9.8 Hz), 5.42 (1H, d, J=8.3 Hz), 5.64 (1H, d, J=5.4 Hz), 6.57 (1H, d, J=7.8 Hz), 6.68 (1H, d, J=8.3 Hz), 6.82 (2H, d, J=8.8 Hz), 7.13 (2H, d, J=8.3 Hz), 7.19 (1H, t, J=8.3 Hz), 10.28 (1H, s)

74	$CH_3O(CH_2)_2CO$-	M.p. 120.5-122°C FABMS (m/z): 629 [(M+Na)$^+$] NMR (DMSO-d_6) δ : 2.43 (2H, t, J=6.9 Hz), 2.51 (2H, t, J=6.6 Hz), 2.76 (2H, m), 2.93 (2H, m), 3.12 (3H, s), 3.21 (3H, s), 3.4-3.56 (6H, m), 3.63 (1H, m), 3.70 (1H, m), 3.71 (3H, s), 4.72 (1H, t, J=5.6 Hz), 4.90 (1H, dd, J=8.0, 9.9 Hz), 5.14 (1H, dd, J=9.3, 9.6 Hz), 5.39 (1H, d, J=8.0 Hz), 5.53 (1H, d, J=5.8 Hz), 6.56 (1H, d, J=8.0 Hz), 6.67 (1H, d, J=8.2 Hz), 6.82 (2H, ddd, J=2.1, 3.0, 8.7 Hz), 7.13 (2H, ddd, J=2.0, 2.8, 8.7 Hz), 7.19 (1H, t, J=8.3 Hz), 10.38 (1H, s)
75	$CH_3OCH(CH_3)CO$-	FABMS (m/z): 629 [(M+Na)$^+$] NMR (DMSO-d_6) δ : 1.1-1.3 (6H, m), 2.7-2.8 (2H, m), 2.9-3.0 (2H, m), 3.15-3.25 (6H, m), 3.5-3.6 (2H, m), 3.6-3.7 (2H, m), 3.71 (3H, s), 3.8-3.9 (2H, m), 4.74 (1H, brs), 4.97 (1H, t, J=8.5 Hz), 5.22 (1H, t, J=9.6 Hz), 5.5-5.6 (1H, m), 5.66 (1H, d, J=6.1 Hz), 6.56 (1H, dd, J=3.0, 8.2 Hz), 6.67 (1H, dd, J=1.8, 8.3 Hz), 6.83 (2H, d, J=8.7 Hz), 7.14 (1H, d, J=7.7 Hz), 7.16 (1H, t, J=8.5 Hz), 7.20 (1H, t, J=8.3 Hz), 10.31 (1H, s)
76	$CH_3OC(CH_3)_2CO$-	FABMS (m/z): 657 [(M+Na)$^+$] NMR (DMSO-d_6) δ : 1.21 (3H, s), 1.22 (3H, s), 1.29 (3H, s), 1.31 (3H, s), 2.79 (2H, t, J=7.2 Hz), 2.96 (2H, t, J=7.2 Hz), 3.04 (3H, s), 3.15 (3H, s), 3.5-3.6 (2H, m), 3.6-3.7 (2H, m), 3.72 (3H, s), 4.72 (1H, t, J=5.5 Hz), 4.95 (1H, dd, J=7.8. 9.6 Hz), 5.22 (1H, t, J=9.3 Hz), 5.58 (1H, d, J=6.7 Hz), 5.61 (1H, d, J=7.8 Hz), 6.55 (1H, d, J=8.3 Hz), 6.67 (1H, d, J=8.6 Hz), 6.83 (2H, d, J=8.6 Hz), 7.16 (2H, d, J=8.6 Hz), 7.20 (1H, t, J=8.4 Hz), 10.30 (1H, s)

77	CH_3CH_2OCO-	M.p. 117-119°C FABMS (m/z): 601 [(M+Na)+] NMR ($DMSO-d_6$) δ : 1.15 (3H, t, J=7.1 Hz), 1.20 (3H, t, J=7.1 Hz), 2.76 (2H, m), 2.91 (2H, m), 3.4-3.8 (4H, m), 3.71 (3H, s), 3.99 - 4.20 (4H, m), 4.68 (1H, dd, J=7.8, 9.8 Hz), 4.74 (1H, t, J=4.9 Hz), 4.94 (1H, dd, J=8.8, 9.8 Hz), 5.43 (1H, d, J=7.8 Hz), 5.72 (1H, d, J=5.4 Hz), 6.57 (1H, d, J=8.3 Hz), 6.65 (1H, d, J=8.3 Hz), 6.83 (2H, ddd, J=2.0, 3.2, 8.3 Hz), 7.13 (2H, d, J=8.3 Hz), 7.19 (1H, t, J=8.3 Hz), 10.23 (1H, s)
78	$(CH_3)_2CHCH_2OCO$-	FABMS (m/z): 657 [(M+Na)+] NMR ($DMSO-d_6$) δ : 0.80 (6H, dd, J=2.0, 6.8 Hz), 0.87 (6H, d, J=6.8 Hz), 1.84 (2H, m), 2.79 (2H, m), 2.88 (2H, m), 3.4-3.75 (4H, m), 3.70 (3H, s), 3.75-3.95 (4H, m), 4.70 (1H, dd, J=7.8, 9.8 Hz), 4.74 (1H, t, J=5.6 Hz), 4.96 (1H, dd, J=8.8, 9.3 Hz), 5.46 (1H, d, J=7.8 Hz), 5.72 (1H, d, J=5.9 Hz), 6.57 (1H, d, J=8.3 Hz), 6.66 (1H, d, J=8.3 Hz), 6.82 (2H, ddd, J=2.0, 2.9, 8.3 Hz), 7.13 (2H, d, J=8.3 Hz), 7.19 (1H, t, J=8.3 Hz), 10.25 (1H, s)
79		FABMS (m/z): 697 [(M+Na)+] NMR ($DMSO-d_6$) δ : 2.74 (2H, t, J=7.3 Hz), 2.99 (2H, t, J=7.3 Hz), 3.6-3.8 (4H, m), 3.68 (3H, s), 4.82 (1H, t, J=5.9 Hz), 4.86 (1H, dd, J=7.8, 9.3 Hz), 5.15 (1H, dd, J=8.8, 9.3 Hz), 5.60 (1H, d, J=7.8 Hz), 5.97 (1H, d, J=4.9 Hz), 6.61 (1H, d, J=8.3 Hz), 6.71 (1H, d, J=8.3 Hz), 6.77 (2H, ddd, J=2.0, 2.9, 8.8 Hz), 7.05 (2H, ddd, J=2.0, 2.9, 8.3 Hz), 7.1-7.5 (11H, m), 10.25 (1H, s)

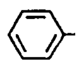
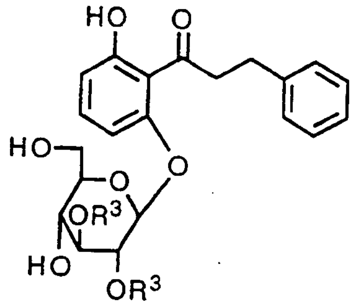
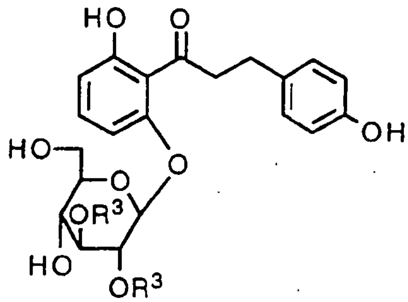
80	$CH_3OCH_2CH_2OCO$-	FABMS (m/z): 661 [$(M+Na)^+$] NMR (DMSO-d_6) δ : 2.7-2.8 (2H, m), 2.9-3.0 (2H, m), 3.21 (3H, s), 3.26 (3H, s), 3.4-3.5 (6H, m), 3.6-3.7 (2H, m), 3.71 (3H, s), 4.1-4.3 (4H, m), 4.70 (1H, dd, J=8.0, 9.8 Hz), 4.74 (1H, t, J=5.5 Hz), 4.96 (1H, t, J=9.6 Hz), 5.44 (1H, d, J=8.0 Hz), 5.74 (1H, d, J=6.0 Hz), 6.57 (1H, d, J=8.3 Hz), 6.65 (1H, d, J=8.5 Hz), 6.83 (2H, dd, J=2.0, 6.5 Hz), 7.14 (2H, d, J=8.7 Hz), 7.19 (1H, t, J=8.4 Hz), 10.28 (1H, s)
81	-$CH_2OCONHCH_2CO$-	FABMS (m/z): 839 [$(M+Na)^+$] NMR (DMSO-d_6) δ : 2.78 (2H, t, J=6.8 Hz), 2.98 (2H, t, J=6.8 Hz), 3.4-4.0 (8H, m), 3.69 (3H, s), 4.73 (1H, t, J=4.9 Hz), 4.92 (1H, dd, J=7.8, 9.8 Hz), 4.98 (2H, s), 5.05 (2H, s), 5.18 (1H, dd, J=8.8, 9.8 Hz), 5.44 (1H, d, J=7.8 Hz), 5.59 (1H, d, J=4.9 Hz), 6.57 (1H, d, J=8.3 Hz), 6.69 (1H, d, J=8.3 Hz), 6.80 (2H, ddd, J=2.2, 2.9, 8.8 Hz), 7.14 (2H, d, J=8.3 Hz), 7.21 (1H, t, J=8.3 Hz), 7.30 (10H, m), 7.50 (2H, m), 10.57 (1H, broad)
82	$CH_3SO_3H\cdot NH_2CH_2CO$-	FABMS (m/z): 571 [$(M+Na)^+$] NMR (DMSO-d_6) δ : 2.40 (6H, s), 2.81 (2H, t, J=7.1 Hz), 3.02 (2H, t, J=7.1 Hz), 3.4-3.5 (4H, m), 3.72 (3H, s), 3.83 (4H, m), 4.30 (2H, broad), 4.96 (1H, dd, J=8.3, 9.8 Hz), 5.28 (1H, dd, J=8.8, 9.8 Hz), 5.45 (1H, d, J=7.8 Hz), 6.61 (1H, d, J=8.3 Hz), 6.70 (1H, d, J=8.3 Hz), 6.83 (2H, d, J=8.8 Hz), 7.16 (2H, d, J=8.8 Hz), 7.23 (1H, t, J=8.3 Hz), 8.30 (6H, broad), 10.46 (1H, broad)

Table 11



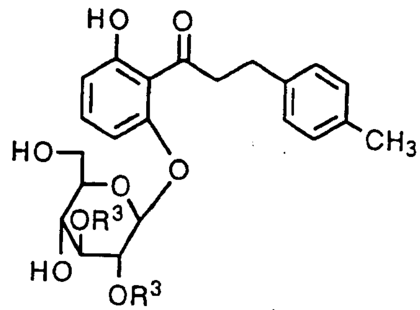
Ex. No.	R^3	Physical properties
83	CH_3CO-	FABMS (m/z): 511 [(M+Na)+] NMR (DMSO-d_6) δ : 1.91 (3H, s), 1.99 (3H, s), 2.8 - 3.0 (4H, m), 3.4-3.8 (4H, m), 4.73 (1H, t, J=5.9 Hz), 4.86 (1H, dd, J=8.3, 9.8 Hz), 5.09 (1H, t, J=9.8 Hz), 5.36 (1H, d, J=7.8 Hz), 5.56 (1H, t, J=5.4 Hz), 6.57 (1H, d, J=8.3 Hz), 6.67 (1H, d, J=8.3 Hz), 7.1-7.3 (6H, m), 10.26 (1H, s)
84	CH_3OCH_2CO-	M.p. 100-102°C FABMS (m/z): 571 [(M+Na)+] NMR (DMSO-d_6) δ : 2.8-3.0 (4H, m), 3.26 (3H, s), 3.29 (3H, s), 3.5-3.7 (4H, m), 3.92 (2H, dd, J=9.3, 16.6 Hz), 4.08 (2H, dd, J=9.3, 16.6 Hz), 4.75 (1H, t, J=5.8 Hz), 4.93 (1H, dd, J=8.3, 9.8 Hz), 5.19 (1H, t, J=9.8 Hz), 5.43 (1H, d, J=7.8 Hz), 5.64 (1H, t, J=4.9 Hz), 6.57 (1H, d, J=7.8 Hz), 6.68 (1H, t, J=8.3 Hz), 7.1-7.3 (6H, m), 10.27 (1H, s)

Table 12



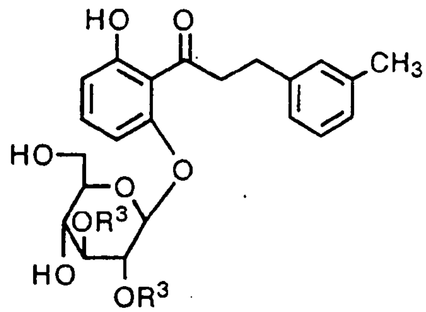
Ex. No.	R^3	Physical properties
85	CH_3OCH_2CO-	FABMS (m/z): 587 [(M+Na)+] NMR (DMSO-d_6) δ : 2.70 (2H, m), 2.89 (2H, m), 3.26 (3H, s), 3.29 (3H, s), 3.4-3.8 (4H, m), 3.92 (2H, dd, J=9.8, 16.6 Hz), 4.07 (2H, dd, J=9.0, 16.8 Hz), 4.75 (1H, t, J=5.4 Hz), 4.93 (1H, dd, J=8.1, 9.5 Hz), 5.19 (1H, dd, J=8.8, 9.8 Hz), 5.43 (1H, d, J=7.8 Hz), 5.64 (1H, d, J=5.4 Hz), 6.57 (1H, d, J=7.8 Hz), 6.65 (1H, d, J=8.3 Hz), 6.68 (1H, d, J=8.3 Hz), 7.00 (2H, d, J=8.3 Hz), 7.19 (1H, t, J=8.3 Hz), 9.11 (1H, s), 10.26 (1H, s)
86	$CH_3CH_2OCH_2CO$-	M.p. 111-114.5°C FABMS (m/z): 615 [(M+Na)+] NMR (DMSO-d_6) δ : 1.07 (3H, t, J=6.8 Hz), 1.12 (3H, t, J=6.8 Hz), 2.70 (2H, m), 2.90 (2H, m), 3.3-3.8 (8H, m), 3.95 (2H, dd, J=10.0, 16.8 Hz), 4.10 (2H, dd, J=8.8, 16.6 Hz), 4.75 (1H, t, J=5.6 Hz), 4.91 (1H, dd, J=8.1, 9.5 Hz), 5.18 (1H, dd, J=8.8, 9.3 Hz), 5.42 (1H, d, J=7.8 Hz), 5.63 (1H, d, J=5.4 Hz), 6.57 (1H, d, J=7.8 Hz), 6.65 (2H, d, J=8.3 Hz), 6.68 (1H, d, J=8.3 Hz), 7.00 (2H, d, J=8.3 Hz), 7.19 (1H, t, J=8.3 Hz), 9.11 (1H, s), 10.27 (1H, s)
87	CH_3CO-	M.p. 141.5-143°C FABMS (m/z): 527 [(M+Na)+] IR (nujol) cm^{-1}: 3440, 3240, 1750, 1630
88	CH_3CH_2OCO-	M.p. 145-147.5°C FABMS (m/z): 587 [(M+Na)+] IR (nujol) cm^{-1}: 3400, 3280, 1770, 1750, 1630

Table 13



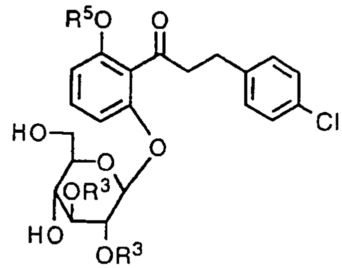
Ex. No.	R^3	Physical properties
89	CH_3CO-	M.p. 84-87°C FABMS (m/z): 525 [(M+Na)+] NMR (DMSO-d_6) δ : 1.91 (3H, s), 2.00 (3H, s), 2.25 (3H, s), 2.78 (2H, m), 2.89 (2H, m), 3.4-3.75 (4H, m), 4.73 (1H, t, J=5.6 Hz), 4.85 (1H, dd, J=7.8, 9.8 Hz), 5.09 (1H, dd, J=8.8, 9.8 Hz), 5.35 (1H, d, J=7.8 Hz), 5.56 (1H, d, J=5.4 Hz), 6.57 (1H, d, J=8.3 Hz), 6.67 (1H, d, J=8.3 Hz), 7.06 (2H, d, J=8.8 Hz), 7.11 (2H, d, J=8.8 Hz), 7.18 (1H, t, J=8.3 Hz), 10.26 (1H, s)
90	CH_3OCH_2CO-	FABMS (m/z): 585 [(M+Na)+] NMR (DMSO-d_6) δ : 2.25 (3H, s), 2.77 (2H, m), 2.93 (2H, m), 3.26 (3H, s), 3.29 (3H, s), 3.4-3.8 (4H, m), 3.92 (2H, dd, J=9.5, 16.9 Hz), 4.07 (2H, dd, J=8.0, 16.9 Hz), 4.75 (1H, t, J=5.4 Hz), 4.92 (1H, dd, J=7.8, 9.8 Hz), 5.19 (1H, dd, J=8.8, 9.8 Hz), 5.43 (1H, d, J=8.3 Hz), 5.64 (1H, d, J=4.9 Hz), 6.57 (1H, d, J=8.3 Hz), 6.68 (1H, d, J=8.3 Hz), 7.06 (2H, dd, J=2.4, 8.8 Hz), 7.11 (2H, dd, J=2.9, 8.8 Hz), 7.19 (1H, t, J=8.3 Hz), 10.27 (1H, s)

Table 14



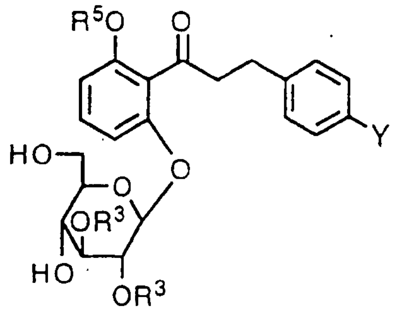
Ex. No.	R^3	Physical properties
91	CH_3CO-	M.p. 106-107°C FABMS (m/z): 525 [(M+Na)$^+$] NMR (DMSO-d_6) δ : 1.91 (3H, s), 1.99 (3H, s), 2.27 (3H, s), 2.7-2.8 (2H, m), 2.9-3.0 (2H, m), 3.4-3.5 (2H, m), 3.6-3.8 (2H, m), 4.72 (1H, t, J=5.8 Hz), 4.86 (1H, dd, J=8.0, 10.0 Hz), 5.09 (1H, t, J=9.4 Hz), 5.34 (1H, d, J=8.0 Hz), 5.56 (1H, d, J=5.6 Hz), 6.57 (1H, d, J=8.1 Hz), 6.68 (1H, d, J=8.2 Hz), 6.9-7.0 (3H, m), 7.15 (1H, t, J=7.5 Hz), 7.19 (1H, t, J=8.3 Hz), 10.30 (1H, s)
92	$CH_3CH_2OCH_2CO$-	FABMS (m/z): 613 [(M+Na)$^+$] NMR (DMSO-d_6) δ : 1.07 (3H, t, J=7.0 Hz), 1.12 (3H, t, J=7.0 Hz), 2.27 (3H, s), 2.7-2.8 (2H, m), 2.9-3.0 (2H, m), 3.4-3.6 (6H, m), 3.6 - 3.7 (2H, m), 3.95 (2H, dd, J=15.0, 16.8 Hz), 4.09 (2H, dd, J=11.5, 16.8 Hz), 4.75 (1H, t, J=5.5 Hz), 4.92 (1H, dd, J=8.0, 9.7 Hz), 5.18 (1H, t, J=9.3 Hz), 5.42 (1H, d, J=7.9 Hz), 5.63 (1H, d, J=5.5 Hz), 6.58 (1H, d, J=8.2 Hz), 6.69 (1H, d, J=8.4 Hz), 6.98 (1H, d, J=7.8 Hz), 7.0 - 7.1 (2H, m), 7.15 (1H, t, J=7.4 Hz), 7.19 (1H, t, J=8.3 Hz), 10.30 (1H, s)

Table 15

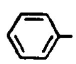
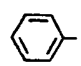


Ex. No.	R^3	R^5	Physical properties
93	CH_3CO-	CH_3CO-	FABMS (m/z): 587/589 [(M+Na)+] NMR (DMSO-d_6) δ : 1.90 (3H, s), 2.00 (3H, s), 2.05 (3H, s), 2.82 (2H, m), 2.98 (2H, m), 3.47-3.77 (4H, m), 4.75 (1H, t, J=5.7 Hz), 4.88 (1H, dd, J=7.9, 9.9 Hz), 5.12 (1H, dd, J=9.3, 9.6 Hz), 5.51 (1H, d, J=8.0 Hz), 5.59 (1H, d, J=5.6 Hz), 6.88 (1H, d, J=8.1 Hz), 7.16 (1H, d, J=8.1 Hz), 7.26 (2H, ddd, J=2.1, 2.2, 8.7 Hz), 7.34 (2H, ddd, J=2.1, 2.3, 8.6 Hz), 7.45 (1H, t, J=8.3 Hz)
94	CH_3CO-	H-	M.p. 119-120.5°C FABMS (m/z): 545/547 [(M+Na)+] NMR (DMSO-d_6) δ : 1.92 (3H, s), 2.00 (3H, s), 2.83 (2H, m), 2.95 (2H, m), 3.45 - 3.76 (4H, m), 4.73 (1H, t, J=5.6 Hz), 4.85 (1H, dd, J=8.0, 9.8 Hz), 5.09 (1H, t, J=9.4 Hz), 5.36 (1H, d, J=8.0 Hz), 5.55 (1H, d, J=5.6 Hz), 6.57 (1H, d, J=8.2 Hz), 6.68 (1H, d, J=8.5 Hz), 7.19 (1H, t, J=8.3 Hz), 7.26 (2H, dd, J=2.2, 8.6 Hz), 7.32 (2H, ddd, J=2.1, 2.2, 8.6 Hz), 10.28 (1H, s)
95	CH_3OCH_2CO-	H-	FABMS (m/z): 605/607 [(M+Na)+] NMR (DMSO-d_6) δ : 2.82 (2H, m), 2.97 (2H, m), 3.26 (3H, s), 3.29 (3H, s), 3.47 - 3.77 (4H, m), 3.93 (2H, dd, J=14.1, 16.9 Hz), 4.07 (2H, dd, J=8.7, 16.9 Hz), 4.75 (1H, t, J=5.6 Hz), 4.92 (1H, dd, J=8.0, 9.8 Hz), 5.19 (1H, t, J=9.3 Hz), 5.43 (1H, d, J=8.0 Hz), 5.64 (1H, d, J=5.5 Hz), 6.57 (1H, d, J=8.2 Hz), 6.68 (1H, d, J=8.2 Hz), 7.19 (1H, t, J=8.3 Hz), 7.26 (2H, ddd, J=2.1, 2.4, 8.7 Hz), 7.31 (2H, ddd, J=2.0, 2.2, 8.7 Hz), 10.29 (1H, s)

Table 16



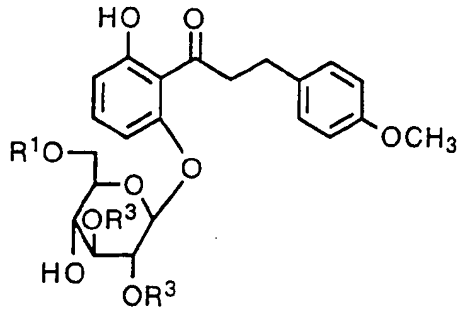
Ex. No.	Y, R^3, R^5	Physical properties
96	Y: CH_3COO- R^3: CH_3CO- R^5: H-	M.p. 127-129°C FABMS (m/z): 569 [$(M+Na)^+$] NMR (DMSO-d_6) δ : 1.91 (3H, s), 1.99 (3H, s), 2.24 (3H, s), 2.85 (2H, m), 2.95 (2H, m), 3.4 - 3.8 (4H, m), 4.73 (1H, t, J=5.4 Hz), 4.86 (1H, dd, J=8.3, 9.8 Hz), 5.09 (1H, dd, J=8.8, 9.8 Hz), 5.36 (1H, d, J=7.8 Hz), 5.56 (1H, d, J=5.4 Hz), 6.57 (1H, d, J=7.8 Hz), 6.67 (1H, d, J=8.3 Hz), 7.01 (2H, ddd, J=1.7, 2.7, 8.3 Hz), 7.19 (1H, t, J=8.3 Hz), 7.26 (2H, dd, J=2.0, 8.3 Hz), 10.27 (1H, s)
97	Y: CH_3CH_2OCOO- R^3: CH_3CO- R^5: H-	FABMS (m/z): 599 [$(M+Na)^+$] NMR (DMSO-d_6) δ : 1.28 (3H, t, J=7.1 Hz), 1.91 (3H, s), 1.99 (3H, s), 2.85 (2H, m), 2.96 (2H, m), 3.4-3.8 (4H, m), 4.23 (2H, q, J=7.1 Hz), 4.73 (1H, t, J=5.4 Hz), 4.86 (1H, dd, J=7.8, 9.8 Hz), 5.09 (1H, dd, J=8.8, 9.8 Hz), 5.36 (1H, d, J=7.8 Hz), 5.56 (1H, d, J=5.4 Hz), 6.57 (1H, d, J=8.3 Hz), 6.67 (1H, d, J=8.3 Hz), 7.11 (2H, d, J=8.3 Hz), 7.19 (1H, t, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz), 10.27 (1H, s)

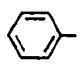
98	Y: CH_3CH_2OCOO- R^3: CH_3OCH_2CO- R^5: H-	FABMS (m/z): 659 [(M+Na)+] NMR (DMSO-d_6) δ : 1.28 (3H, t, J=7.1 Hz), 2.84 (2H, m), 2.98 (2H, m), 3.26 (3H, s), 3.29 (3H, s), 3.4-3.8 (4H, m), 3.92 (2H, dd, J=9.5, 16.8 Hz), 4.08 (2H, dd, J=5.9, 16.6 Hz), 4.23 (2H, q, J=7.1 Hz), 4.75 (1H, t, J=5.6 Hz), 4.93 (1H, dd, J=7.8, 9.8 Hz), 5.19 (1H, dd, J=8.8, 9.8 Hz), 5.43 (1H, d, J=7.8 Hz), 5.64 (1H, d, J=4.9 Hz), 6.57 (1H, d, J=8.3 Hz), 6.68 (1H, d, J=8.3 Hz), 7.11 (2H, ddd, J=2.0, 2.7, 8.3 Hz), 7.19 (1H, t, J=8.3 Hz), 7.27 (2H, dd, J=2.0, 8.8 Hz), 10.28 (1H, s)
99 (Reference)	Y: CH_3O- R^3: -CH_2OCOO— R^5: -CH_2OCO—	FABMS (m/z): 859 [(M+Na)+] NMR (DMSO-d_6) δ : 2.7-3.1 (4H, m), 3.5-3.8 (4H, m), 3.65 (3H, s), 4.77 (1H, t, J=5.2 Hz), 4.78 (1H, dd, J=7.9, 9.8 Hz), 5.0-5.2 (5H, m), 5.23 (2H, s), 5.64 (1H, d, J=7.8 Hz), 5.80 (1H, d, J=6.0 Hz), 6.78 (2H, dd, J=2.2, 8.8 Hz), 7.06 (1H, d, J= 8.4 Hz), 7.09 (2H, d, J=8.8 Hz), 7.18 (1H, d, J=8.4 Hz), 7.25-7.43 (15H, m), 7.49 (1H, t, J=8.3 Hz)

Example 100

[0097] 4-Methoxy-6'-hydroxy-2'-O-β-D-glucopyranosyldihydrochalcone (1.30 g) is dissolved in pyridine (13 ml), and thereto is added dropwise with stirring benzoyl chloride (0.90 g) under ice-cooling over a period of 30 minutes. The mixture is stirred under ice-cooling for two hours, and poured into ice-water. The mixture is extracted with ethyl acetate, and the organic layer is washed with water, dried, filtered, and concentrated. The residue is purified by silica gel column chromatography (solvent; chloroform/methanol) to give 4-methoxy-6'-hydroxy-2'-O-(6-O-benzoyl-β-D-glucopyranosyl)dihydrochalcone (0.80 g) as colorless amorphous powders. The physical properties of this compound are shown in Table 17.

Table 17



Ex. No.	R^1	R^3	Physical properties
100	 -CO—	H-	FABMS (m/z): 561 [(M+Na)$^+$] NMR (DMSO-d_6) δ : 2.7-2.8 (2H, m), 3.1 - 3.4 (5H, m), 3.70 (3H, s), 3.6-3.8 (1H, m), 4.27 (1H, dd, J=7.3, 11.7 Hz), 4.60 (1H, d, J=10.3 Hz), 5.01 (1H, d, J=6.8 Hz), 5.26 (1H, d, J=4.4 Hz), 5.36 (1H, d, J=4.9 Hz), 5.40 (1H, d, J=4.9 Hz), 6.52 (1H, d, J= 8.3 Hz), 6.68 (1H, d, J=8.3 Hz), 6.79 (2H, d, J=8.8 Hz), 7.0-7.1 (1H, m), 7.13 (2H, d, J=8.8 Hz), 7.5-7.7 (3H, m), 7.95 (2H, dd, J=1.5, 6.8 Hz), 10.86 (1H, s)

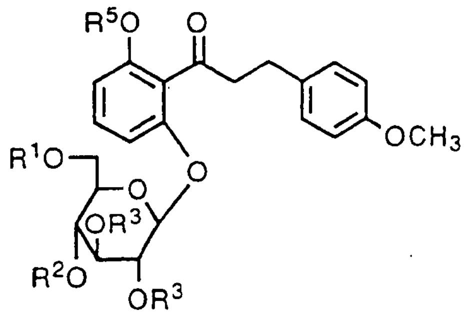
Example 101

[0098] 4-Methoxy-6'-hydroxy-2'-O-β-D-glucopyranosyldihydrochalcone (1.0 g) is dissolved in pyridine (20 ml), and thereto is added acetic anhydride (5 ml). The mixture is stirred at room temperature for two days, and concentrated. To the residue are added ethyl acetate and diluted hydrochloric acid, and the mixture is stirred. The organic layer is collected, washed with water, dried, filtered, and concentrated. The residue is purified by silica gel column chromatography (solvent; chloroform/ethyl acetate) to give 4-methoxy-6'-acetoxy-2'-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)dihydrochalcone (1.21 g) as white powders. The physical properties of this compound are shown in Table 18.

Example 102

[0099] 4-Methoxy-6'-hydroxy-2'-O-β-D-glucopyranosyldihydrochalcone (869 mg) is dissolved in pyridine (10 ml), and thereto is added dropwise with stirring methoxyacetic chloride (1.30 g) under ice-cooling. The mixture is reacted at room temperature for two hours, and concentrated under reduced pressure. To the residue are added ethyl acetate and ice-cold diluted hydrochloric acid, and the mixture is stirred. The organic layer is collected, washed with water, dried, filtered, and concentrated. The residue is dissolved in methanol (20 ml), and thereto is added sodium hydrogen carbonate (840 mg). The mixture is stirred at room temperature for 30 minutes, and thereto is added ethyl acetate (100 ml). The insoluble materials are removed by filtration, and the filtrate is washed with water, dried, filtered, and concentrated. The residue is purified by silica gel column chromatography (solvent; chloroform/methanol) to give 4-methoxy-6'-hydroxy-2'-O-(2,3,4,6-tetra-O - methoxyacetyl-β-D-glucopyranosyl)dihydrochalcone (882 mg) as pale yellow oil. The physical properties of this compound are shown in Table 18.

Table 18



Ex. No.	R^1, R^2, R^3, R^5	Physical properties
101	R^1, R^2, R^3: CH_3CO- R^5: CH_3CO-	M.p. 60-63°C FABMS (m/z): 667 [(M+Na)+] NMR (DMSO-d_6) δ : 1.94 (3H, s), 1.97 (3H, s), 2.01 (6H, s), 2.06 (3H, s), 2.75 (2H, m), 2.89 (2H, m), 3.71 (3H, s), 4.06 - 4.31 (3H, m), 5.01 (1H, dd, J=9.3, 9.8 Hz), 5.06 (1H, dd, J=8.2, 9.8 Hz), 5.41 (1H, dd, J=9.3, 9.8 Hz), 5.63 (1H, d, J=7.8 Hz), 6.84 (2H, ddd, J=2.0, 2.9, 8.8 Hz), 6.93 (1H, d, J=8.3 Hz), 7.10 (1H, d, J=7.8 Hz), 7.14 (2H, d, J=8.7 Hz), 7.48 (1H, t, H=8.3 Hz)
102	R^1, R^2; R^3: CH_3OCH_2CO- R^5: H-	FABMS (m/z): 745 [(M+Na)+] NMR (DMSO-d_6) δ : 2.6-3.1 (4H, m), 3.25 (3H, s), 3.27 (3H, s), 3.28 (6H, s), 3.32 (3H, s), 3.25-3.9 (9H, m), 4.33 (2H, m), 5.11 (2H, m), 5.53 (1H, dd, J=9.3, 9.8 Hz), 5.58 (1H, d, J=7.8 Hz), 6.60 (1H, d, J=7.8 Hz), 6.62 (1H, d, J=8.3 Hz), 6.83 (2H, d, J=8.8 Hz), 7.13 (2H, d, J=8.8 Hz), 7.21 (1H, t, J=8.3 Hz), 10.25 (1H, s)

Example 103 (Reference)

[0100] Using 4,6'-dimethoxy-2'-O-β-D-glucopyranosyldihydrochalcone, there is obtained 4,6'-dimethoxy-2'-O-(4,6-O-benzylidene-β-D-glucopy ranosyl)dihydrochalcone in the same manner as in Example 56.

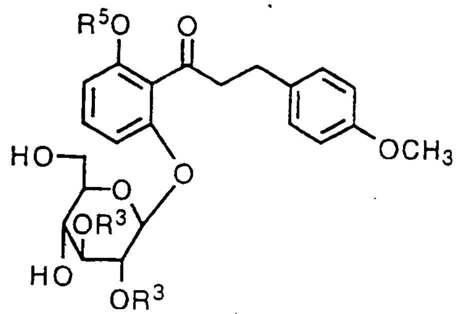
FABMS (m/z): 559 [(M+Na)+]

NMR (DMSO-d_6) δ : 2.81 (2H, t, J=8.3 Hz), 2.9-3.8 (7H, m), 3.715 (3H, s), 3.721 (3H, s), 4.19 (1H, dd, J=3.4, 8.6 Hz), 5.14 (1H, d, J=7.7 Hz), 5.45 (1H, d, J=5.3 Hz), 5.55 (1H, d, J=4.9 Hz), 5.58 (1H, s), 6.76 (1H, d, J=8.4 Hz), 6.84 (2H, ddd, J=2.0, 3.0, 8.6 Hz), 6.86 (1H, d, J=8.4 Hz), 7.15 (2H, dd, J=2.1, 8.7 Hz), 7.32 (1H, t, J=8.4 Hz), 7.4-7.5 (5H, m)

Examples 104-105

[0101] Using 4,6'-dimethoxy-2'-O-(4,6-O-benzylidene-β-D-glucopyranosyl) - dihydrochalcone, the compounds listed in Table 19 are obtained in the same manner as in Examples 63-(1) and 64 or Example 65.

Table 19



Ex. No.	R^3, R^5	Physical properties
104	R^3: CH_3CO- R^5: CH_3-	NMR (DMSO-d_6) δ : 1.91 (3H, s), 2.00 (3H, s), 2.7 - 3.0 (4H, m), 3.5-3.7 (4H, m), 3.71(3H, s), 3.72 (3H, s), 4.74 (1H, t, J=5.8 Hz), 4.84 (1H, dd, J=8.0, 9.9 Hz), 5.08 (1H, dd, J=9.3, 9.6 Hz), 5.34 (1H, d, J=8.0 Hz), 5.56 (1H, d, J=5.6 Hz), 6.77 (1H, d, J=8.3 Hz), 6.83 (2H, dd, J=2.1, 8.7 Hz), 6.84 (1H, d, J=8.5 Hz), 7.13 (2H, ddd, J=2.1, 2.9, 8.7 Hz), 7.32 (1H, t, J=8.4 Hz) FABMS (m/z): 555 [(M+Na)+]
105	R^3: CH_3OCH_2CO- R^5: CH_3-	NMR (DMSO-d_6) δ : 2.75 (2H, m), 2.84 (2H, m), 3.27 (3H, s), 3.29 (3H, s), 3.4-3.8 (4H, m), 3.71 (6H, s), 3.93 (2H, dd, J=14.2, 16.9 Hz), 4.06 (2H, dd, J=14.8, 16.8 Hz), 4.76 (1H, t, J=5.7 Hz), 4.91 (1H, dd, J=8.0, 9.9 Hz), 5.19 (1H, dd, J=9.2, 9.6 Hz), 5.42 (1H, d, J=8.0 Hz), 5.64 (1H, d, J=5.5 Hz), 6.78 (1H, d, J=8.3 Hz), 6.83 (2H, ddd, J=2.2, 3.0, 8.8 Hz), 6.85 (1H, d, J=8.2 Hz), 7.12 (2H, ddd, J=2.0, 2.9, 8.7 Hz), 7.33 (1H, t, J=8.4 Hz) FABMS (m/z): 615 [(M+Na)+]

Example 106

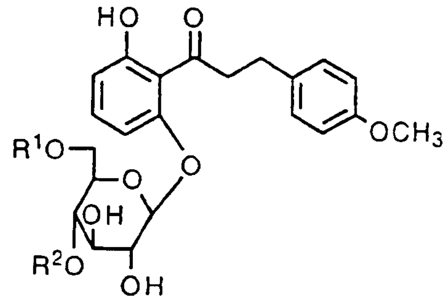
[0102] The compound obtained in Reference Example 99 (569 mg) is dissolved in pyridine (5 ml), and thereto is added acetic anhydride (278 mg). The mixture is stirred at room temperature for two hours, and concentrated under reduced pressure. To the residue is added ethyl acetate, and the organic layer is washed with water, dried, and evaporated to remove the solvent. The residue is dissolved in a mixture of ethanol-ethyl acetate (5 ml/5 ml), and the mixture is subjected to catalytic hydrogenation under atmospheric pressure by using 10 % palladium-carbon. The catalyst is removed by filtration, and the filtrate is evaporated to remove the solvent. The residue is purified by silica gel column chromatography (solvent; chloroform/methanol) to give 4-methoxy-6'-hydroxy-2'-O-(4,6-di-O-acetyl-β-D-glucopyranosyl)dihydrochalcone (251 mg).

M.p. 108-112°C
FABMS (m/z): 519 (MH^+)
NMR (DMSO-d_6) δ : 1.94 (3H, s), 2.05 (3H, s), 2.83 (2H, t, J=7.1 Hz), 3.18 (2H, m), 3.32 (1H, m), 3.53 (1H, m), 3.71 (3H, s), 3.90 (1H, m), 3.96 (1H, dd, J=2.2, 12.4 Hz), 4.09 (1H, dd, J=5.7, 12.0 Hz), 4.69 (1H, dd, J=9.5, 9.8 Hz), 5.08 (1H, d, J=7.8 Hz), 5.47 (1H, d, J=5.7 Hz), 5.58 (1H, d, J=5.6 Hz), 6.57 (1H, d, J=8.1 Hz), 6.66 (1H, d, J=8.1 Hz), 6.82 (2H, ddd, J=2.1, 3.0, 8.7 Hz), 7.16 (2H, ddd, J=2.0, 3.0, 8.6 Hz), 7.24 (1H, t, J=8.3 Hz), 10.82 (1H, s)

Examples 107-109

[0103] Using the corresponding starting compounds, the compounds listed in Table 20 are obtained in the same manner as in Example 106.

Table 20



Ex. No.	R^1, R^2	Physical properties
107	R^1: CH_3OCH_2CO- R^2: CH_3OCH_2CO-	NMR (DMSO-d_6) δ : 2.83 (2H, t, J=7.0 Hz), 3.18 (2H, t, J=7.0 Hz), 3.25 (3H, s), 3.32 (3H, s), 3.33 (1H, m), 3.55 (1H, m), 3.71 (3H, s), 3.93 (2H, d, J=16.7 Hz), 4.01 (2H, d, J=16.7 Hz), 4.0-4.1 (2H, m), 4.22 (1H, m), 4.75 (1H, dd, J=9.5, 9.9 Hz), 5.11 (1H, d, J=7.9 Hz), 5.53 (1H, d, J=5.7 Hz), 5.61 (1H, d, J=5.7 Hz), 6.57 (1H, d, J=8.1 Hz), 6.66 (1H, d, J=8.1 Hz), 6.82 (2H, ddd, J=2.1, 3.0, 8.7 Hz), 7.16 (2H, ddd, J=2.1, 2.9, 8.7 Hz), 7.24 (1H, t, J=8.3 Hz), 10.80 (1H, s) FABMS (m/z): 579 [(M+Na)+]
108	R^1: $CH_3CH_2OCH_2CO$- R^2: $CH_3CH_2OCH_2CO$-	NMR (DMSO-d_6) δ : 1.08 (3H, t, J=7.0 Hz), 1.13 (3H, t, J=7.0 Hz), 2.83 (2H, t, J=7.5 Hz), 3.18 (2H, t, J=7.8 Hz), 3.3-3.6 (6H, m), 3.71 (3H, s), 3.9-4.1 (2H, m), 3.96 (1H, d, J=16.7 Hz), 4.03 (1H, d, J=16.7 Hz), 4.12 (2H, s), 4.20 (1H, dd, J=5.4, 12.2 Hz), 4.75 (1H, dd, J=9.6, 9.7 Hz), 5.11 (1H, d, J=7.8 Hz), 5.52 (1H, d, J=5.6 Hz), 5.60 (1H, d, J=5.7 Hz), 6.57 (1H, d, J=7.7 Hz), 6.66 (1H, d, J=8.1 Hz), 6.82 (2H, ddd, J=2.1, 3.0, 8.7 Hz), 7.16 (2H, ddd, J=2.1, 2.9, 8.7 Hz), 7.23 (1H, t, J=8.3 Hz), 10.80 (1H, s) FABMS (m/z): 629 [(M+Na)+]

109	R^1: CH_3CH_2OCO- R^2: CH_3CH_2OCO-	M.p. 89.5-92°C NMR (DMSO-d_6) δ : 1.17 (3H, t, J=7.1 Hz), 1.23 (3H, t, J=7.1 Hz), 2.83 (2H, t, J=7.0 Hz), 3.17 (2H, m), 3.31 (1H, m), 3.54 (1H, m), 3.71 (3H, s), 3.97 (1H, m), 4.06 (2H, q, J=7.1 Hz), 4.1-4.2 (4H, m), 4.50 (1H, dd, J=9.6, 9.8 Hz), 5.10 (1H, d, J=7.9 Hz), 5.57 (1H, d, J=6.0 Hz), 5.62 (1H, d, J=5.7 Hz), 6.57 (1H, d, J=8.1 Hz), 6.65 (1H, d, J=8.1 Hz), 6.82 (2H, ddd, J=2.1, 3.0, 8.8 Hz), 7.16 (2H, ddd, J=2.0, 3.0, 8.7 Hz), 7.22 (1H, t, J=8.3 Hz), 10.83 (1H, s) FABMS (m/z): 601 [$(M+Na)^+$]

Reference Example 1

[0104] A mixture of 2',6'-dihydroxyacetophenone (1.065 g), cadmium carbonate (4.83 g) and toluene (100 ml) is refluxed while the solvent is removed by using a Dien-Stark trap. After 30 ml of the solvent is removed, 2,3,6-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-β-D-glucopyranosyl bromide (11.42 g) is added to the mixture, and the mixture is refluxed for 17 hours. After cooling, the insoluble materials are removed by filtration, and the filtrate is concentrated. The residue is purified by silica gel column chromatography to give 2'-O-[2,3,6-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-β-D-glucopyranosyl]-6'-hydroxyacetophenone (4.30 g).

IR (nujol) cm^{-1}: 1750, 1630
NMR ($CDCl_3$) δ : 2.01 (3H, s), 2.03 (6H, s), 2.04 (3H, s), 2.06 (3H, s), 2.08 (3H, s), 2.10 (3H, s), 2.59 (3H, s), 3.8-4.35 (6H, m), 4.46 (1H, dd, J=2.9, 12.2 Hz), 4.87 (1H, dd, J=4.2, 10.5 Hz), 5.06 (1H, t, J=9.8 Hz), 5.21 (1H, d, J=7.3 Hz), 5.32 (1H, d, J=2.5 Hz), 5.35-5.47 (3H, m), 6.49 (1H, d, J=8.3 Hz), 6.71 (1H, d, J=8.3 Hz), 7.36 (1H, t, J=8.3 Hz), 12.96 (1H, s)
FABMS (m/z): 793 [$(M+Na)^+$]

Reference Example 2

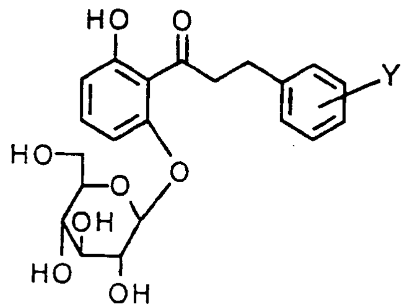
[0105] To a mixture or 6'-hydroxy-2'-O-(2,3,4,6-tetra-O-acetyly-β-D-glucopyranosyl)acetophenone (2.41 g), p-anisaldehyde (1.36 g) and ethanol (25 ml) is added dropwise with stirring a 50 % aqueous potassium hydroxide solution (2.5 ml), and the mixture is stirred at room temperature overnight. The mixture is concentrated under reduced pressure, and to the resulting residue are added water (100 m) and diethyl ether (50 ml), and the mixture is stirred. The aqueous layer is collected, and neutralized with a 10 % hydrochloric acid under ice-cooling, and thereto is added ethyl acetate (200 ml). The mixture is stirred, and the organic layer is collected, washed with water, dried, and filtered. The filtrate is concentrated under reduced pressure, and the residue is dissolved in ethanol (50 ml). The mixture is subjected to catalytic hydrogenation under atmospheric pressure with 10 % palladium-carbon. The catalyst is removed by filtration, and the filtrate is concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform/methanol) to give 4-methoxy-6'-hydroxy-2'-O-β-D-glucopyranosyl-dihydrochalcone (1.02 g) as white crystalline powders.

M.p. 127-129°C
FABMS (m/z): 435 (MH^+)
NMR (DMSO-d_6) δ : 2.84 (2H, t, J=7.3 Hz), 3.19-3.49 (7H, m), 3.7 (1H, m), 3.71 (3H, s), 4.56 (1H, t, J=5.4 Hz), 4.91 (1H, d, J=7.3 Hz), 5.03 (1H, d, J=4.9 Hz), 5.10 (1H, d, J=4.4 Hz), 5.22 (1H, d, J=4.9 Hz), 6.55 (1H, d, J=8.3 Hz), 6.67 (1H, d, J=8.3 Hz), 6.81 (2H, d, J=8.8 Hz), 7.17 (2H, d, J=8.8 Hz), 7.24 (1H, t, J=8.3 Hz), 10.99 (1H, s)

Reference Examples 3-4

[0106] Using the corresponding starting compounds, the compounds listed in Table 21 are obtained in the same manner as in Reference Example 2.

Table 21



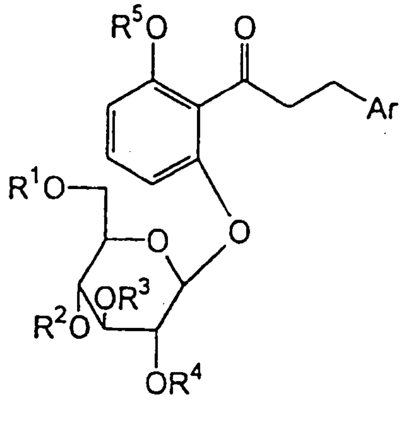
Ref. Ex. No.	Y	Physical properties
3	4-HO-	M.p. 171-174°C NMR (DMSO-d_6) δ : 2.78 (2H, t, J=7.6 Hz), 3.20 (2H, t, J=7.6 Hz), 3.1-3.5 (5H, m), 3.70 (1H, dd, J=4.6, 11.0 Hz), 4.56 (1H, t, J=5.6 Hz), 4.91 (1H, d, J=6.8 Hz), 5.03 (1H, d, J=4.9 Hz), 5.09 (1H, d, J=3.9 Hz), 5.22 (1H, d, J=4.9 Hz), 6.54 (1H, d, J=8.3 Hz), 6.64 (2H, d, J=8.8 Hz), 6.67 (1H, d, J=8.3 Hz), 7.03 (2H, d, J=8.3 Hz), 7.24 (1H, t, J=8.3 Hz), 9.09 (1H, bro), 11.00 (1H, bro) IR (nujol) cm^{-1}: 3600-3000, 1620 FABMS (m/z): 443 [$(M+Na)^+$], 421 (MH^+)
4	H-	M.p. 126-129°C NMR (DMSO-d_6) δ : 2.90 (2H, t, J=7.6 Hz), 3.23 (2H, t, J=7.8 Hz), 3.1-3.5 (5H, m), 3.70 (1H, dd, J=5.1, 10.5 Hz), 4.55 (1H, t, J=5.6 Hz), 4.91 (1H, d, J=7.3 Hz), 5.02 (1H, d, J=4.9 Hz), 5.09 (1H, d, J=4.4 Hz), 5.23 (1H, d, J=5.4 Hz), 6.55 (1H, d, J=8.3 Hz), 6.68 (1H, d, J=8.3 Hz), 7.11-7.28 (6H, m), 10.97 (1H, s) IR (nujol) cm^{-1}: 3480-3280, 1630 FABMS (m/z): 405 (MH^+)

Effects of the Invention

[0107] The dihydrochalcone derivatives [I], which are active ingredients of the present invention, have urine glucose increasing activity being based on the inhibitory activity of renal glucose reabsorption thereof, by which they show excellent hypoglycemic activity. In addition, the dihydrochalcone derivatives [I] are hardly hydrolyzed at the intestine unlike phlorizin, and hence, they can be used in the prophylaxis or treatment of diabetes either by oral administration or by parenteral administration. Moreover, the active dihydrochalcone derivatives [I] have low toxicity, and the aglycone, a hydrolysate thereof, show extremely weak inhibitory effect on the glucose-uptake, and hence, the active dihydrochalcone derivatives [I] and pharmaceutically acceptable salts thereof show high safety as medicine.

Claims

1. The use of a dihydrochalcone derivative of the formula [I]:



[I]

wherein Ar is 1) a phenyl group optionally substituted by 1 to 2 groups selected from a C_{1-6} alkyl group; a trihalogeno-C_{1-6} alkyl group; a C_{1-6} alkoxy group optionally substituted by a C_{1-6} alkoxy group; a C_{1-6} alkoxy)-carbonyloxy group optionally substituted by a C_{1-6} alkoxy group; a dialkylamino group; a C_{2-7} alkanoyloxy group optionally substituted by a C_{1-6} alkoxy group, a (C_{1-6} alkoxy)-carbonyl group or an amino group; a halogen atom; a hydroxy group; a C_{1-6} alkylthio group; a phenoxycarbonyloxy group; a C_{1-6} alkylenedioxy group; and a benzoyloxy group optionally substituted by a C_{1-6} alkoxy group; 2) a furyl group; 3) a thienyl group; or 4) a naphthyl group, R^1 is a hydrogen atom; a C_{2-7} alkanoyl group optionally substituted by a C_{1-6} alkoxy group; a (C_{1-6} alkoxy)-carbonyl group; or a benzoyl group, R^2 is a hydrogen atom; a C_{2-7} alkanoyl group optionally substituted by a C_{1-6} alkoxy group; a C_{1-6} alkoxy)-carbonyl group; or a α-D-glucopyranosyl group, R^3 and R^4 are each a hydrogen atom; a C_{2-7} alkanoyl group optionally substituted by a group selected from a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, and an amino group; a (C_{1-6} alkoxy)-carbonyl group optionally substituted by a C_{1-6} alkoxy group; a benzoyl group; or a phenoxycarbonyl group, and the group of the formula OR^5 is a protected or unprotected hydroxy group or a C_{1-6} alkoxy group, provided that when R^1, R^2, R^3 and R^4 are hydrogen atoms and OR^5 is a hydroxy group, Ar is different from a 4-hydroxyphenyl group, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for preventive or therapeutic application to diabetes.

2. The use according to claim 1, wherein Ar is a phenyl group, a C_{1-6} alkyl-substituted phenyl group, a C_{1-6} alkoxy-substituted phenyl group, a (C_{1-6} alkoxy)-carbonyloxy-substituted phenyl group or a halogenophenyl group, the group of the formula OR^5 is a protected or unprotected hydroxy group, and R^1, R^2, R^3 and R^4 are each a hydrogen atom.

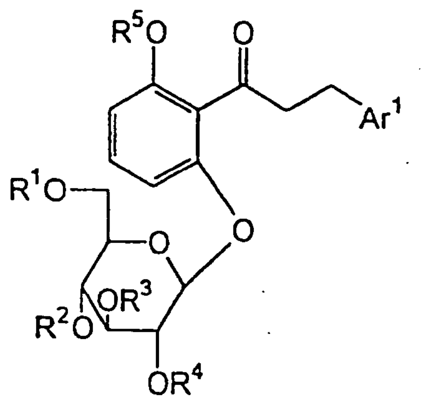
3. The use according to claim 1, wherein Ar is a phenyl group optionally substituted by a group selected from a halogen atom; a hydroxy group; a C_{1-6} alkyl group; a C_{1-6} alkoxy group; a C_{2-7} alkanoyloxy group; and a (C_{1-6} alkoxy)-carbonyloxy group, the group of the formula OR^5 is a protected or unprotected hydroxy group or a C_{1-6} alkoxy group, R^1 and R^2 are both a hydrogen atom, and R^3 and R^4 are each a C_{2-7} alkanoyl group optionally substituted by a group selected from a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, and an amino group; a (C_{1-6} alkoxy)-carbonyl group; a benzoyl group; or a phenoxycarbonyl group.

4. The use according to claim 3, wherein Ar is a phenyl group optionally substituted by a C_{1-6} alkyl group or a C_{1-6} alkoxy group, the group of the formula: OR^5 is a hydroxy group or a hydroxy group protected by a C_{2-7} alkanoyl group, R^1 and R^2 are both hydrogen atoms, and R^3 and R^4 are each a C_{2-7} alkanoyl group, a C_{1-6} alkoxy-substituted C_{2-7} alkanoyl group, an amino-substituted C_{2-7} alkanoyl group, a (C_{1-6} alkoxy)-carbonyl group or phenoxycarbonyl group.

5. The use according to claim 4, wherein Ar is a C_{1-6} alkoxy-substituted phenyl group, and R^3 and R^4 are each a C_{1-6} alkoxy-substituted C_{2-7} alkanoyl group.

6. The use according to anyone of claim 1 to 5, wherein said medicament is for oral administration.

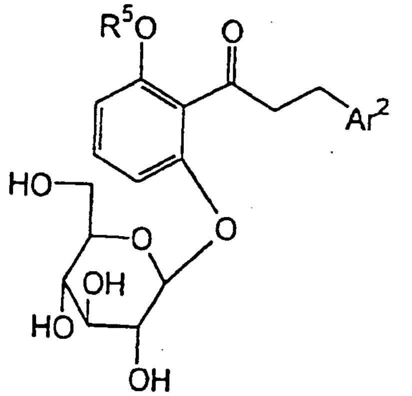
7. A dihydrochalcone derivative of the formula [I-A]:



[I-A]

wherein R^1, R^2, R^3, R^4 and OR^5 are the same as defined in Claim 1 and Ar' is Ar_4 as defined in claim 1, provided that when R^1, R^2, R^3 and R^4 are hydrogen atoms and OR^5 is a hydroxy group, Ar' is different from a 4-hydroxyphenyl group, 4-methoxyphenyl group and phenyl group, or a pharmaceutically acceptable salt thereof.

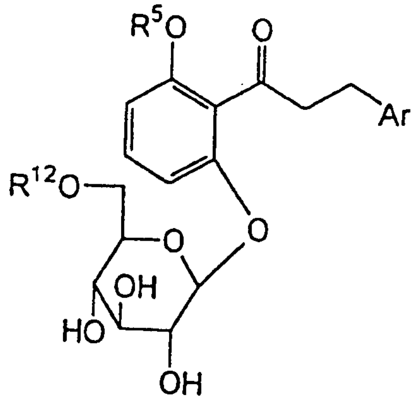
8. A compound of the formula [I-a]:



[I-a]

wherein Ar^2 is 1) a phenyl group substituted by 1 to 2 groups selected from a C_{1-6} alkyl group; a trihalogeno-C_{1-6} alkyl group; a C_{1-6} alkoxy group (other than 4-methoxy group) optionally substituted by a C_{1-6} alkoxy group; a (C_{1-6} alkoxy)-carbonyloxy group optionally substituted by a C_{1-6} alkoxy group; a dialkylamino group; a C_{2-7} alkanoyloxy group optionally substituted by a C_{1-6} alkoxy group, a (C_{1-6} alkoxy)-carbonyl group or an amino group; a halogen atom; a hydroxy group other than 4- hydroxy group; a C_{1-6} alkylthio group; a phenoxycarbonyloxy group; a C_{1-6} alkylenedioxy group; and a benzoyloxy group optionally substituted by a C_{1-6} alkoxy group; 2) a furyl group; 3) a thienyl group; or 4) a naphthyl group, and the group of the formula OR^5 is a protected or unprotected hydroxy group or a C_{1-6} alkoxy group, or a pharmaceutically acceptable salt thereof.

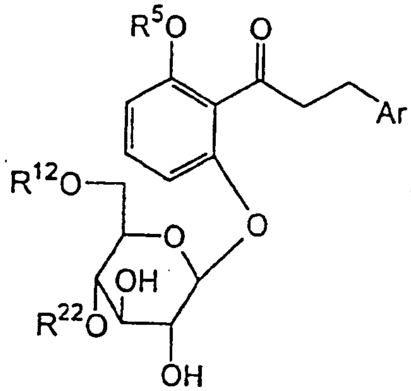
9. A compound of the formula [I-c]:



[I-c]

wherein Ar is 1) a phenyl group optionally substituted by 1 to 2 groups selected from a C_{1-6} alkyl group; a trihalogeno-C_{1-6} alkyl group; a C_{1-6} alkoxy group optionally substituted by a C_{1-6} alkoxy group; a C_{1-6} alkoxy)-carbonyloxy group optionally substituted by a C_{1-6} alkoxy group; a dialkylamino group; a C_{2-7} alkanoyloxy group optionally substituted by a C_{1-6} alkoxy group, a (C_{1-6} alkoxy)-carbonyl group or an amino group; a halogen atom; a hydroxy group; a C_{1-6} alkylthio group; a phenoxycarbonyloxy group; a C_{1-6} alkylenedioxy group; and a benzoyloxy group optionally substituted by a C_{1-6} alkoxy group; 2) a furyl group; 3) a thienyl group; or 4) a naphthyl group, R^{12} is a C_{2-7} alkanoyl group optionally substituted by a C_{1-6} alkoxy group; a (C_{1-6} alkoxy)-carbonyl group; or a benzoyl group, and the group of the formula OR^5 is a protected or unprotected hydroxy group or a C_{1-6} alkoxy group, or a pharmaceutically acceptable salt thereof.

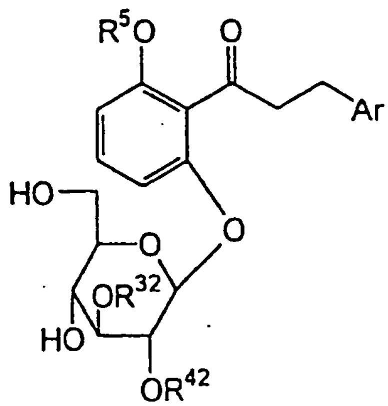
10. A compound of the formula [I-d]:



[I-d]

wherein Ar, R^{12} and OR^5 are the same as defined in Claim 9, R^{22} is a C_{2-7} alkanoyl group optionally substituted by a C_{1-6} alkoxy group; or a (C_{1-6} alkoxy)-carbonyl group or a pharmaceutically acceptable salt thereof.

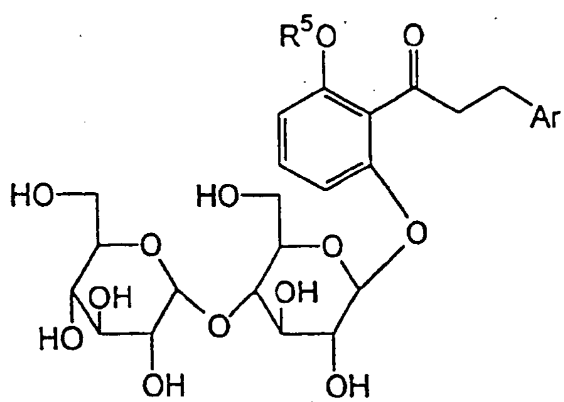
11. A compound of the formula [I-e]:



[I-e]

wherein Ar and OR^5 are the same as defined in Claim 9 and R^{32} and R^{42} are each a C_{2-7} alkanoyl group optionally substituted by a group selected from a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, and an amino group; a (C_{1-6} alkoxy)-carbonyl group optionally substituted by a C_{1-6} alkoxy group; a benzoyl group; or a phenoxycarbonyl group, or a pharmaceutically acceptable salt thereof.

12. A compound of the formula [I-g]:



[I-g]

wherein Ar and OR^5 are the same as defined in claim 9, or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 9, wherein Ar is a phenyl group optionally substituted by a group selected from a halogen atom; a hydroxy group; a C_{1-6} alkyl group; a C_{1-6} alkoxy group; a C_{2-7} alkanoyloxy group; and a (C_{1-6} alkoxy)-carbonyloxy group, the group of the formula OR^5 is a protected or unprotected hydroxy group or a C_{1-6} alkoxy group, and R^{12} is a C_{2-7} alkanoyl group optionally substituted by a C_{1-6} alkoxy group; a (C_{1-6} alkoxy)-carbonyl group; or a benzoyl group.

14. The compound according to claim 10, wherein Ar, R^{12} and OR^5 are the same as defined in claim 13 and R^{22} is a C_{2-7} alkanoyl group optionally substituted by a C_{1-6} alkoxy group; or a (C_{1-6} alkoxy)-carbonyl group.

15. The compound according to claim 11, wherein Ar and OR^5 are the same as defined in claim 13 and R^{32} and R^{42} are each a C_{2-7} alkanoyl group optionally substituted by a group selected from a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, and an amino group; a (C_{1-6} alkoxy)-carbonyl group optionally substituted by a C_{1-6} alkoxy group; a benzoyl group; or a phenoxycarbonyl group.

16. The compound according to claim 12, wherein Ar is a phenyl group, a (C_{1-6} alkyl)-phenyl group, a halogenophenyl

group, a hydroxyphenyl group or a (C_{1-6} alkoxy)-phenyl group, and the group of the formula OR^5 is a protected or unprotected hydroxy group or a C_{1-6} alkoxy group.

17. The compound according to claim 8, wherein Ar^2 is a (C_{1-3} alkyl)-phenyl group, a (C_{2-3} alkoxy)-phenyl group, a (C_{1-6} alkoxy)-carbonyloxyphenyl group, or a halogenophenyl group, and the group of the formula OR^5 is a protected or unprotected hydroxy group.

18. The compound according to claim 15, wherein OR^5 is a protected or unprotected hydroxy group. and R^{32} and R^{42} are each a C_{2-7} alkanoyl group optionally substituted by a group selected from a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, and an amino group; a (C_{1-6} alkoxy)-carbonyl group; a benzoyl group; or a phenoxycarbonyl group.

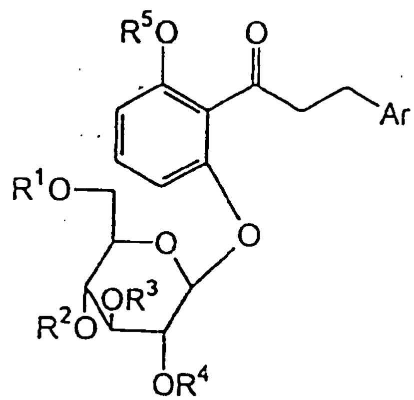
19. The compound according to claim 18, wherein Ar is a phenyl group optionally substituted by a C_{1-6} alkyl group or a C_{1-6} alkoxy group, the group of the formula OR^5 is a hydroxy group or a hydroxy group protected by a C_{2-7} alkanoyl group, and R^{32} and R^{42} are each a C_{2-7} alkanoyl group, a C_{1-6} alkoxy-substituted C_{2-7} alkanoyl group, an amino-substituted C_{2-7} alkanoyl group, a (C_{1-6} alkoxy)-carbonyl group or a phenoxycarbonyl group.

20. The compound according to claim 19, wherein Ar is a C_{1-6} alkoxy-substituted phenyl group, and R^{32} and R^{42} are each a C_{1-6} alkoxy-substituted C_{2-7} alkanoyl group.

21. A pharmaceutical composition which comprises a therapeutically effective amount of a compound as set forth in any of the claims 7 to 20 or a pharmaceutically acceptable salt thereof in admixture with a conventional pharmaceutically acceptable carrier or diluent.

Patentansprüche

1. Verwendung eines Dihydrochalcon-Derivates der Formel [I]:



[I]

worin gilt:

Ar ist 1) eine Phenylgruppe, die gegebenenfalls mit 1 bis 2 Gruppen substituiert ist, ausgewählt aus einer C_{1-6}-Alkyl-, Trihalogen-C_{1-6}-alkyl-, C_{1-6}-Alkoxygruppe, die gegebenenfalls mit einer C_{1-6}-Alkoxygruppe substituiert ist, einer (C_{1-6}-Alkoxy)carbonyloxygruppe, die gegebenenfalls mit einer C_{1-6}-Alkoxygruppe substituiert ist, einer Dialkylaminogrupe, einer C_{2-7}-Alkanoyloxygruppe, die gegebenenfalls mit einer C_{1-6}-Alkoxy-, (C_{1-6}Alkoxy)carbonyl- oder einer Aminogruppe substituiert ist, einem Halogenatom, einer Hydroxy-, C_{1-6}-Alkylthio-, Phenoxycarbonyloxy-, C_{1-6}-Alkylendioxy- und aus einer Benzoyloxygruppe, die gegebenenfalls mit einer C_{1-6}-Alkoxygruppe substituiert ist,
2) eine Furylgruppe,
3) eine Thienylgruppe oder
4) eine Naphthylgruppe;
R^1 ist ein Wasserstoffatom, eine C_{2-7}-Alkanoylgruppe, die gegebenenfalls mit einer C_{1-6}-Alkoxygruppe substituiert ist, eine (C_{1-6}-Alkoxy)-carbonyl- oder eine Benzoylgruppe;

R^2 ist ein Wasserstoffatom, eine C_{2-7}-Alkanoylgruppe, die gegebenenfalls mit einer C_{1-6}-Alkoxygruppe substituiert ist, eine (C_{1-6}-Alkoxy)-carbonyl- oder eine α-D-Glucopyranosylgruppe;

R^3 und R^4 sind jeweils ein Wasserstoffatom, eine C_{2-7}-Alkanoylgruppe, die gegebenenfalls mit einer Gruppe substituiert ist, ausgewählt aus einer C_{1-6}-Alkoxy-, C_{1-6}-Alkoxy-C_{1-6}-alkoxy- und aus einer Aminogruppe, eine (C_{1-6}-Alkoxy)carbonylgruppe, die gegebenenfalls mit einer C_{1-6}-Alkoxygruppe substituiert ist, eine Benzoyl- oder eine Phenoxycarbonylgruppe; und

die Gruppe der Formel OR^5 ist eine geschützte oder ungeschützte Hydroxygruppe oder eine C_{1-6}-Alkoxygruppe,

mit der Maßgabe, dass,

wenn R^1, R^2, R^3 und R^4 Wasserstoffatome und OR^5 eine Hydroxygruppe sind, Ar von einer 4-Hydroxyphenylgruppe verschieden ist,

oder eines pharmazeutisch geeigneten Salzes davon,

zur Herstellung eines Medikaments zur präventiven oder therapeutischen Anwendung gegenüber Diabetes.

2. Verwendung gemäß Anspruch 1, worin Ar eine Phenyl-, C_{1-6}-Alkyl-substituierte Phenyl-, C_{1-6}-Alkoxy-substituierte Phenyl-, (C_{1-6}-Alkoxy)carbonyloxy-substituierte Phenyl- oder eine Halogenophenylgruppe, die Gruppe der Formel OR^5 eine geschützte oder ungeschützte Hydroxygruppe und R^1, R^2, R^3 und R^4 jeweils ein Wasserstoffatom sind.

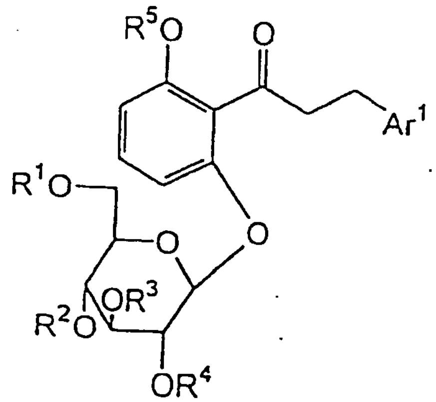
3. Verwendung gemäss Anspruch 1, worin Ar eine Phenylgruppe, die gegebenenfalls mit einer Gruppe substituiert ist, ausgewählt aus einem Halogenatom, einer Hydroxy-, C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, C_{2-7}-Alkanoyloxy- und aus einer (C_{1-6}-Alkoxy)carbonyloxygruppe, die Gruppe der Formel OR^5 eine geschützte oder ungeschützte Hydroxy- oder eine C_{1-6}-Alkoxygruppe, R^1 und R^2 beide ein Wasserstoffatom und R^3 und R^4 jeweils eine C_{2-7}-Alkanoyl-gruppe, die gegebenenfalls mit einer Gruppe substituiert ist, ausgewählt aus einer C_{1-6}-Alkoxy-, C_{1-6}-Alkoxy-C_{1-6}-alkoxy- und aus einer Aminogruppe, eine (C_{1-6}-Alkoxy)carbonyl-, Benzoyl- oder eine Phenoxycarbonylgruppe sind.

4. Verwendung gemäß Anspruch 3, worin Ar eine Phenylgruppe, die gegebenenfalls mit einer C_{1-6}-Alkyl- oder einer C_{1-6}-Alkoxygruppe substituiert ist, die Gruppe der Formel OR^5 eine Hydroxy- oder eine mit einer C_{2-7}-Alkanoylgruppe geschützte Hydroxygruppe, R^1 und R^2 beide Wasser-stoffatome und R^3 und R^4 jeweils eine C_{2-7}-Alkanoyl-, C_{1-6}-Alkoxy-substi-tuierte C_{2-7}-Alkanoyl-, Amino-substituierte C_{2-7}-Alkanoyl-, (C_{1-6}-Alk-oxy)carbonyl- oder eine Phenoxycarbonylgruppe sind.

5. Verwendung gemäß Anspruch 4, worin Ar eine C_{1-6}-Alkoxy-substituierte Phenylgrupe und R^3 und R^4 jeweils eine C_{1-6}-Alkoxy-substituierte C_{2-7}-Alkanoylgruppe sind.

6. Verwendung gemäß einem der Ansprüche 1 bis 5, wobei das genannte Medikament zur oralen Verabreichung vorgesehen ist.

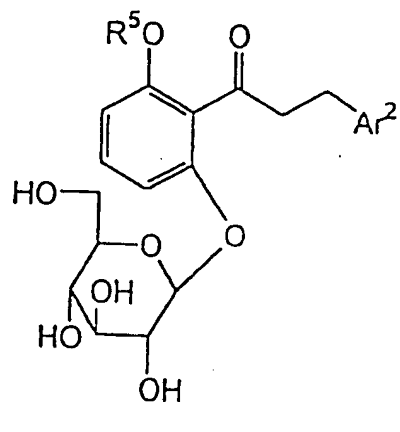
7. Dihydrochalcon-Derivat der Formel [I-A]:



[I-A]

worin R^1, R^2, R^3, R^4 und OR^5 wie in Anspruch 1 definiert und Ar' ein in Anspruch 1 definiertes Ar sind, mit der Maßgabe, dass, wenn R^1, R^2, R^3 und R^4 Wasserstoffatome und OR^5 eine Hydroxygruppe sind, Ar' von einer 4-Hydroxyphenyl-, 4-Methoxyphenyl- und von einer Phenylgruppe verschieden ist, oder ein pharmazeutisch zulässiges Salz davon.

8. Verbindung der Formel [I-a] oder pharmazeutisch zulässiges Salz davon:

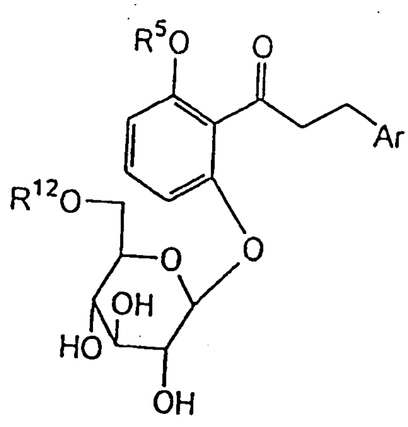


[I-a]

worin gilt:

Ar^2 ist 1) eine Phenylgruppe, die mit 1 bis 2 Gruppen substituiert ist, ausgewählt aus einer C_{1-6}-Alkyl-, Trihalogeno-C_{1-6}-alkyl-, C_{1-6}-Alkoxygruppe (verschieden von der 4-Methoxygruppe), gegebenenfalls substituiert mit einer C_{1-6}-Alkoxygruppe, einer (C_{1-6}-Alkoxy)-carbonylgruppe, gegebenenfalls substituiert mit einer C_{1-6}-Alkoxygruppe, einer Dialkylaminogruppe, einer C_{2-7}-Alkanoyloxygruppe, gegebenenfalls substituiert mit einer C_{1-6}-Alkoxy-, (C_{1-6}-Alkoxy)Carbonyl oder mit einer Aminogruppe, einem Halogenatom, einer Hydroxygruppe, die sich von der 4-Hydroxygruppe unterscheidet, einer C_{1-6}-Alkylthio-, Phenoxycarbonyloxy-, C_{1-6}-Alkenyldioxy- und aus einer Benzoyloxygruppe, gegebenenfalls substituiert mit einer C_{1-6}-Alkoxygruppe,
2) eine Furylgruppe,
3) eine Thienylgruppe oder
4) eine Naphthylgruppe; und
die Gruppe der Formel OR^5 ist eine geschützte oder ungeschützte Hydroxy- oder eine C_{1-6}-Alkoxygruppe.

9. Verbindung der Formel [I-c] oder pharmazeutisch zulässiges Salz davon:



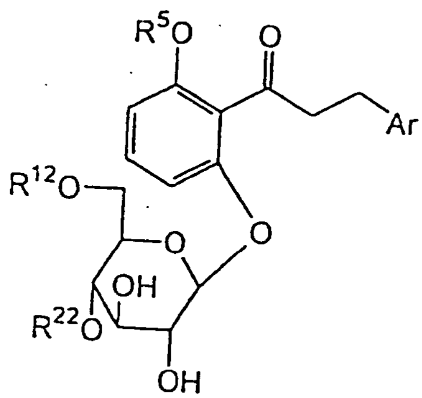
[I-c]

worin gilt:

Ar ist 1) eine Phenylgruppe, die gegebenenfalls mit 1 bis 2 Gruppen substituiert ist, ausgewählt aus einer C_{1-6}-Alkyl-, Trihalogen-C_{1-6}-alkyl-, gegebenenfalls mit einer C_{1-6}-Alkoxygruppe substituierten C_{1-6}-Alkoxy-, gege-

benenfalls mit einer C_{1-6}-Alkoxygruppe substituierten (C_{1-6}-Alk oxy)carbonyloxy-, Dialkylamino-, gegebenenfalls mit einer C_{1-6}-Alkoxy-gruppe substituierten C_{2-7}-Alkanoyloxy-, (C_{1-6}-Alkoxy)carbonyl- oder aus einer Aminogruppe, einem Halogenatom, einer Hydroxy-, C_{1-6}-Alkylthio-, Phenoxycarbonyloxy-, C_{1-6}-Alkylendioxy- und aus einer gegebenenfalls mit einer C_{1-6}-Alkoxygruppe substituierten Benzoyloxygruppe,
2) eine Furylgruppe, 3) eine Thienylgruppe oder 4) eine Naphthylgruppe;
R^{12} ist eine gegebenenfalls mit einer C_{1-6}-Alkoxygruppe substituierte C_{2-7}-Alkanoylgruppe, (C_{1-6}-Alkoxy)carbonyl- oder eine Benzoylgruppe;
und die Gruppe der Formel OR^5 ist eine geschützte oder ungeschützte Hydroxy- oder eine C_{1-6}-Alkoxygruppe.

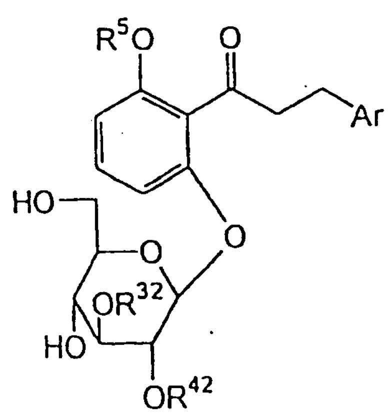
10. Verbindung der Formel [I-d]:



[I-d]

worin Ar, R^{12} und OR^5 wie in Anspruch 9 definiert und R^{22} eine gegebenenfalls mit einer C_{1-6}-Alkoxygruppe substituierte C_{2-7}-Alkanoyl- oder eine C_{1-6}-Alkoxycarbonylgruppe sind,
oder ein pharmazeutisch zulässiges Salz davon.

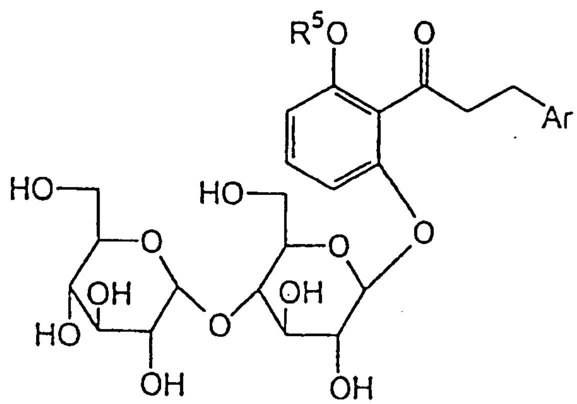
11. Verbindung der Formel [I-e]:



[I-e]

worin Ar und OR^5 wie in Anspruch 9 definiert und R^{32} und R^{42} jeweils eine C_{2-7}-Alkanoylgruppe, die gegebenenfalls mit einer Gruppe substituiert ist, ausgewählt aus einer C_{1-6}-Alkoxy-, C_{1-6}-Alkoxy-C_{1-6}-alkoxy- und aus einer Aminogruppe, eine (C_{1-6}-Alkoxy)carbonylgruppe, die gegebenenfalls mit einer C_{1-6}-Alkoxygruppe substituiert ist, eine Benzoyl- oder Phenoxycarbonylgruppe sind,
oder ein pharmazeutisch zulässiges Salz davon.

12. Verbindung der Formel [I-g]:



[I-g]

worin Ar und OR^5 wie in Anspruch 9 definiert sind, oder ein pharmazeutisch zulässiges Salz davon.

13. Verbindung gemäß Anspruch 9, worin Ar eine Phenylgruppe, die gegebenenfalls mit einer Gruppe substituiert ist, ausgewählt aus einem Halogenatom, einer Hydroxy-, C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, C_{2-7}-Alkanoyloxy- und aus einer (C_{1-6}-Alkoxy)carbonylgruppe, die Gruppe der Formel OR^5 eine geschützte oder ungeschützte Hydroxy- oder eine C_{1-6}-Alkoxygruppe und R^{12} eine C_{2-7}-Alkanoylgruppe, die gegebenenfalls mit einer C_{1-6}-Alkoxygruppe substituiert ist, eine (C_{1-6}-Alkoxy)carbonyl- oder eine Benzoylgruppe sind.

14. Verbindung gemäß Anspruch 10, worin Ar, R^{12} und OR^5 wie in Anspruch 13 definiert und R^{22} eine C_{2-7}-Alkanoylgruppe, die gegebenenfalls mit einer C_{1-6}-Alkoxygruppe substituiert ist, oder eine (C_{1-6}-Alkoxy)carbonylgruppe sind.

15. Verbindung gemäß Anspruch 11, worin Ar und OR^5 wie in Anspruch 13 definiert und R^{32} und R^{42} jeweils eine C_{2-7}-Alkanoylgruppe, die gegebenenfalls mit einer Gruppe substituiert ist, ausgewählt aus einer C_{1-6}-Alkoxy-, C_{1-6}-Alkoxy-(C_{1-6})alkoxy- und aus einer Aminogruppe, eine (C_{1-6}-Alkoxy)carbonylgruppe, die gegebenenfalls mit einer C_{1-6}-Alkoxygruppe substituiert ist, eine Benzoyl- oder Phenoxycarbonylgruppe sind.

16. Verbindung gemäß Anspruch 12, worin Ar eine Phenyl-, (C_{1-6}-Alkyl)phenyl-, Halogenophenyl-, Hydroxyphenyl- oder eine (C_{1-6}-Alkoxy)phenylgruppe und die Gruppe der Formel OR^5 eine geschützte oder ungeschützte Hydroxygruppe oder eine C_{1-6}-Alkoxygruppe sind.

17. Verbindung gemäß Anspruch 8, worin Ar^2 eine (C_{1-3}-Alkyl)phenyl-, (C_{2-3}-Alkoxy)phenyl-, (C_{1-6}-Alkoxy)carbonyloxyphenyl- oder eine Halogenophenylgruppe und die Gruppe der Formel OR^5 eine geschützte oder ungeschützte Hydroxygruppe sind.

18. Verbindung gemäß Anspruch 15, worin OR^5 eine geschützte oder ungeschützte Hydroxygruppe und R^{32} und R^{42} jeweils eine C_{2-7}-Alkanolgruppe, die gegebenenfalls mit einer Gruppe substituiert ist, ausgewählt aus einer C_{1-6}-Alkoxy-, C_{1-6}-Alkoxy- und aus einer Aminogruppe, eine (C_{1-6}-Alkoxy)carbonyl-, Benzoyl- oder eine Phenoxycarbonylgruppe sind.

19. Verbindung gemäss Anspruch 18, worin Ar eine gegebenenfalls mit einer C_{1-6}-Alkyl- oder C_{1-6}-Alkoxygruppe substituierte Phenylgruppe, die Gruppe der Formel OR^5 eine Hydroxygruppe oder eine mit einer C_{2-7}-Alkanoylgruppe geschützte Hydroxygruppe und R^{32} und R^{42} jeweils eine C_{2-7}-Alkanoyl-, C_{1-6}-Alkoxy-substituierte C_{2-7}-Alkanoyl-, Amino-substituierte C_{2-7}-Alkanoyl-, (C_{1-6}-Alkoxy)carbonyl oder eine Phenoxycarbonylgruppe sind.

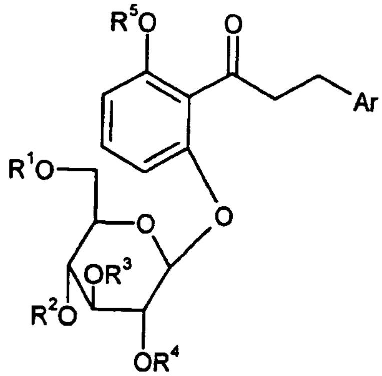
20. Verbindung gemäß Anspruch 19, worin Ar eine C_{1-6}-Alkoxy-substituierte Phenylgruppe und R^{32} und R^{42} jeweils eine C_{1-6}-Alkoxy-substituierte C_{2-7}-Alkanoylgruppe sind.

21. Pharmazeutische Zusammensetzung, die eine therapeutisch wirksame Menge einer Verbindung gemäß einem der

Ansprüche 7 bis 20 oder ein pharmazeutisch zulässiges Salz davon in Abmischung mit einem herkömmlichen pharmazeutisch zulässigen Träger oder Verdünnungsmittel umfasst.

Revendications

1. Utilisation d'un dérivé de dihydrochalcone de formule [I] :



[I]

dans laquelle Ar est 1) un groupe phényle éventuellement substitué par 1 à 2 groupes choisis parmi un groupe alkyle en C_1 à C_6 ; un groupe trihalogéno (alkyle en C_1 à C_6) ; un groupe alcoxy en C_1 à C_6 éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; un groupe (alcoxy en C_1 à C_6)carbonyloxy éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; un groupe dialkylamino ; un groupe alcanoyloxy en C_2 à C_7 éventuellement substitué par un groupe alcoxy en C_1 à C_6, un groupe (alcoxy en C_1 à C_6)carbonyle ou un groupe amino ; un atome d'halogène ; un groupe hydroxy ; un groupe alkylthio en C_1 à C_6 ; un groupe phénoxycarbonyloxy ; un groupe alkylènedioxy en C_1 à C_6 ; et un groupe benzoyloxy éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; 2) un groupe furyle ; 3) un groupe thiényle ; ou 4) un groupe naphtyle, R^1 est un atome d'hydrogène ; un groupe alcanoyle en C_2 à C_7 eventuellement substitué par un groupe alcoxy en C_1 à C_6 ; un groupe (alcoxy en C_1 à C_6)carbonyle ; ou un groupe benzoyle, R^2 est un atome d'hydrogène ; un groupe alcanoyle en C_2 à C_7 éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; un groupe (alcoxy en C_1 à C_6) carbonyle ; ou un groupe α-D-glucopyranosyle, R^3 et R^4 sont chacun un atome d'hydrogène ; un groupe alcanoyle en C_2 à C_7 éventuellement substitué par un groupe choisi parmi un groupe alcoxy en C_1 à C_6, un groupe (alcoxy en C_1 à C_6)alcoxy en C_1 à C_6, et un groupe amino ; un groupe (alcoxy en C_1 à C_6)carbonyle éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; un groupe benzoyle ; ou un groupe phénoxycarbonyle, et le groupe de formule OR^5 est un groupe hydroxy protégé ou non protégé ou un groupe alcoxy en C_1 à C_6, du moment que lorsque R^1, R^2, R^3 et R^4 sont des atomes d'hydrogène et OR^5 est un groupe hydroxy, alors Ar est différent d'un groupe 4-hydroxyphényle, ou d'un sel acceptable en pharmacie de celui-ci, pour la fabrication d'un médicament pour une application préventive ou thérapeutique au diabète.

2. Utilisation selon la revendication 1, dans laquelle Ar est un groupe phényle, un groupe phényle à substitution alkyle en C_1 à C_6, un groupe phényle à substitution alcoxy en C_1 à C_6, un groupe phényle à substitution (alcoxy en C_1 à C_6)carbonyloxy ou un groupe halogénophényle, le groupe de formule OR^5 est un groupe hydroxy protégé ou non protégé, et R^1, R^2, R^3 et R^4 sont chacun un atome d'hydrogène.

3. Utilisation selon la revendication 1, dans laquelle Ar est un groupe phényle éventuellement substitué par un groupe choisi parmi un atome d'halogène ; un groupe hydroxy ; un groupe alkyle en C_1 à C_6 ; un groupe alcoxy en C_1 à C_6 ; un groupe alcanoyloxy en C_2 à C_7 ; et un groupe (alcoxy en C_1 à C_6)carbonyloxy, le groupe de formule OR^5 est un groupe hydroxy protégé ou non protégé ou un groupe alcoxy en C_1 à C_6, R^1 et R^2 sont tous deux un atome d'hydrogène, et R^3 et R^4 sont chacun un groupe alcanoyle en C_2 à C_7 éventuellement substitué par un groupe choisi parmi un groupe alcoxy en C_1 à C_6, un groupe (alcoxy en C_1 à C_6)alcoxy en C_1 à C_6, et un groupe amino ; un groupe (alcoxy en C_1 à C_6)carbonyle ; un groupe benzoyle ; ou un groupe phénoxycarbonyle.

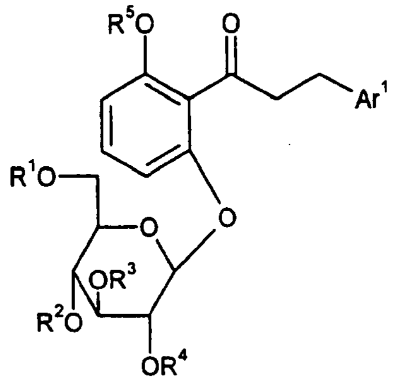
4. Utilisation selon la revendication 3, dans laquelle Ar est un groupe phényle éventuellement substitué par un groupe alkyle en C_1 à C_6 ou un groupe alcoxy en C_1 à C_6, le groupe de formule : OR^5 est un groupe hydroxy ou un groupe hydroxy protégé par un groupe alcanoyle en C_2 à C_7, R^1 et R^2 sont tous deux des atomes d'hydrogène, et R^3 et R^4

sont chacun un groupe alcanoyle en C_2 à C_7, un groupe alcanoyle en C_2 à C_7 à substitution alcoxy en C_1 à C_6, un groupe alcanoyle en C_2 à C_7 à substitution amino, un groupe (alcoxy en C_1 à C_6)carbonyle ou un groupe phénoxycarbonyle.

5. Utilisation selon la revendication 4, dans laquelle Ar est un groupe phényle à substitution alcoxy en C_1 à C_6, et R^3 et R^4 sont chacun un groupe alcanoyle en C_2 à C_7 à substitution alcoxy en C_1 à C_6.

6. Utilisation selon l'une quelconque des revendications 1 à 5, dans laquelle ledit médicament est destiné à une administration par voie orale.

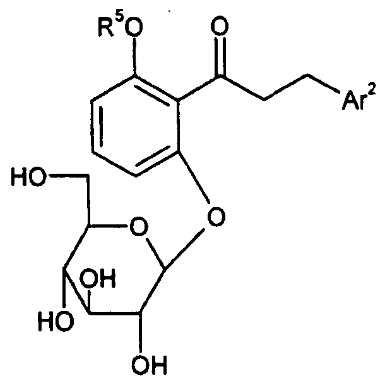
7. Dérivé de dihydrochalcone de formule [I-A] :



[I-A]

dans laquelle R^1, R^2, R^3, R^4 et OR^5 sont les mêmes que ceux définis dans la revendication 1, et Ar^1 est Ar tel que défini dans la revendication 1, du moment que lorsque R^1, R^2, R^3 et R^4 sont des atomes d'hydrogène et OR^5 est un groupe hydroxy, alors Ar^1 est différent d'un groupe 4-hydroxyphényle, d'un groupe 4-méthoxyphényle et d'un groupe phényle, ou un sel acceptable en pharmacie de celui-ci.

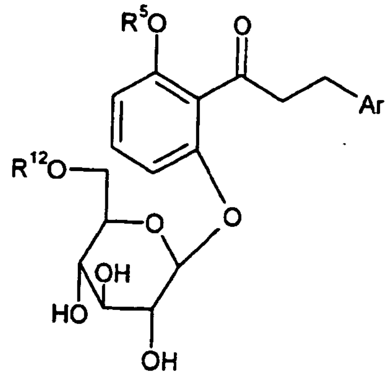
8. Composé de formule [I-a] :



[I-a]

dans laquelle Ar^2 est 1) un groupe phényle substitué par 1 à 2 groupes choisis parmi un groupe alkyle en C_1 à C_6 ; un groupe trihalogéno(alkyle en C_1 à C_6) ; un groupe alcoxy en C_1 à C_6 (autre que le groupe 4-méthoxy) éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; un groupe (alcoxy en C_1 à C_6)carbonyloxy éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; un groupe dialkylamino ; un groupe alcanoyloxy en C_2 à C_7 éventuellement substitué par un groupe alcoxy en C_1 à C_6, un groupe (alcoxy en C_1 à C_6)carbonyle ou un groupe amino ; un atome d'halogène ; un groupe hydroxy autre que le groupe 4-hydroxy ; un groupe alkylthio en C_1 à C_6 ; un groupe phénoxycarbonyloxy ; un groupe alkylènedioxy en C_1 à C_6 ; et un groupe benzoyloxy éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; 2) un groupe furyle ; 3) un groupe thiényle ; ou 4) un groupe naphtyle, et le groupe de formule OR^5 est un groupe hydroxy protégé ou non protégé ou un groupe alcoxy en C_1 à C_6, ou un sel acceptable en pharmacie de celui-ci.

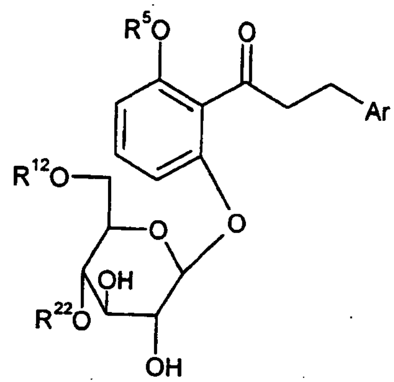
9. Composé de formule [I-c] :



[I-c]

dans laquelle Ar est 1) un groupe phényle éventuellement substitué par 1 à 2 groupes choisis parmi un groupe alkyle en C_1 à C_6 ; un groupe trihalogéno(alkyle en C_1 à C_6) ; un groupe alcoxy en C_1 à C_6 éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; un groupe (alcoxy en C_1 à C_6)carbonyloxy éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; un groupe dialkylamino ; un groupe alcanoyloxy en C_2 à C_7 éventuellement substitué par un groupe alcoxy en C_1 à C_6, un groupe (alcoxy en C_1 à C_6)carbonyle ou un groupe amino ; un atome d'halogène ; un groupe hydroxy ; un groupe alkylthio en C_1 à C_6 ; un groupe phénoxycarbonyloxy ; un groupe alkylènedioxy en C_1 à C_6 ; et un groupe benzoyloxy éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; 2) un groupe furyle ; 3) un groupe thiényle ; ou 4) un groupe naphtyle, R^{12} est un groupe alcanoyle en C_2 à C_7 éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; un groupe (alcoxy en C_1 à C_6)carbonyle ; ou un groupe benzoyle, et le groupe de formule OR^5 est un groupe hydroxy protégé ou non protégé ou un groupe alcoxy en C_1 à C_6, ou un sel acceptable en pharmacie de celui-ci.

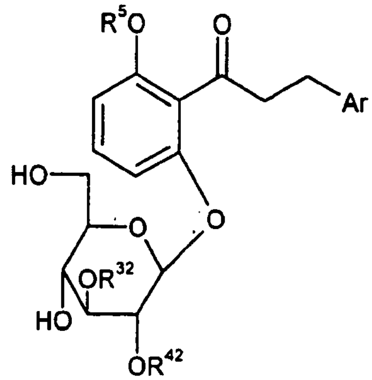
10. Composé de formule [I-d] :



[I-d]

dans laquelle Ar, R^{12} et OR^5 sont les mêmes que ceux définis dans la revendication 9, R^{22} est un groupe alcanoyle en C_2 à C_7 éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; ou un groupe (alcoxy en C_1 à C_6)carbonyle, ou un sel acceptable en pharmacie de celui-ci.

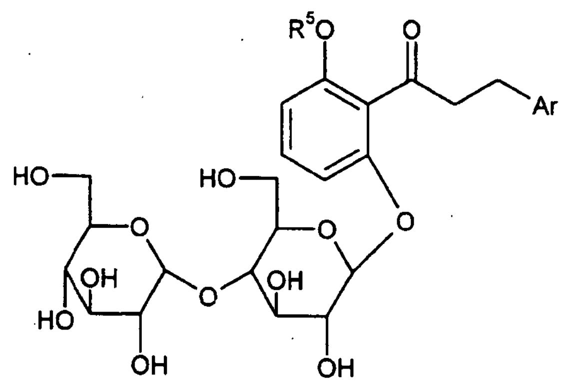
11. Composé de formule [I-e] :



[I-e]

dans laquelle Ar et OR^5 sont les mêmes que ceux définis dans la revendication 9 et R^{32} et R^{42} sont chacun un groupe alcanoyle en C_2 à C_7 éventuellement substitué par un groupe choisi parmi un groupe alcoxy en C_1 à C_6, un groupe (alcoxy en C_1 à C_6)alcoxy en C_1 à C_6, et un groupe amino ; un groupe (alcoxy en C_1 à C_6)carbonyle éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; un groupe benzoyle ; ou un groupe phénoxycarbonyle, ou un sel acceptable en pharmacie de celui-ci.

12. Composé de formule [I-g] :



[I-g]

dans laquelle Ar et OR^5 sont les mêmes que ceux définis dans la revendication 9, ou un sel acceptable en pharmacie de celui-ci.

13. Composé selon la revendication 9, dans lequel Ar est un groupe phényle éventuellement substitué par un groupe choisi parmi un atome d'halogène ; un groupe hydroxy ; un groupe alkyle en C_1 à C_6 ; un groupe alcoxy en C_1 à C_6 ; un groupe alcanoyloxy en C_2 à C_7 ; et un groupe (alcoxy en C_1 à C_6)carbonyloxy, le groupe de formule OR^5 est un groupe hydroxy protégé ou non protégé ou un groupe alcoxy en C_1 à C_6, et R^{12} est un groupe alcanoyle en C_2 à C_7 éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; un groupe (alcoxy en C_1 à C_6)carbonyle ; ou un groupe benzoyle.

14. Composé selon la revendication 10, dans lequel Ar, R^{12} et OR^5 sont les mêmes que ceux définis dans la revendication 13 et R^{22} est un groupe alcanoyle en C_2 à C_7 éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; ou un groupe (alcoxy en C_1 à C_6)carbonyle.

15. Composé selon la revendication 11, dans lequel Ar et OR^5 sont les mêmes que ceux définis dans la revendication 13 et R^{32} et R^{42} sont chacun un groupe alcanoyle en C_2 à C_7 éventuellement substitué par un groupe choisi parmi un groupe alcoxy en C_1 à C_6, un groupe (alcoxy en C_1 à C_6)alcoxy en C_1 à C_6, et un groupe amino ; un groupe (alcoxy en C_1 à C_6)carbonyle éventuellement substitué par un groupe alcoxy en C_1 à C_6 ; un groupe benzoyle ; ou un groupe phénoxycarbonyle.

16. Composé selon la revendication 12, dans lequel Ar est un groupe phényle, un groupe (alkyl en C_1 à C_6)phényle, un groupe halogénophényle, un groupe hydroxyphényle ou un groupe (alcoxy en C_1 à C_6)phényle, et le groupe de formule OR^5 est un groupe hydroxy protégé ou non protégé ou un groupe alcoxy en C_1 à C_6.

17. Composé selon la revendication 8, dans lequel Ar^2 est un groupe (alkyl en C_1 à C_3)phényle, un groupe alcoxy en C_2 à C_3)phényle, un groupe (alcoxy en C_1 à C_6)carbonyloxyphényle, ou un groupe halogénophényle, et le groupe de formule OR^5 est un groupe hydroxy protégé ou non protégé.

18. Composé selon la revendication 15, dans lequel OR^5 est un groupe hydroxy protégé ou non protégé, et R^{32} et R^{42} sont chacun un groupe alcanoyle en C_2 à C_7 éventuellement substitué par un groupe choisi parmi un groupe alcoxy en C_1 à C_6, un groupe (alcoxy en C_1 à C_6)alcoxy en C_1 à C_6, et un groupe amino ; un groupe (alcoxy en C_1 à C_6)carbonyle ; un groupe benzoyle ; ou un groupe phénoxycarbonyle.

19. Composé selon la revendication 18, dans lequel Ar est un groupe phényle éventuellement substitué par un groupe alkyle en C_1 à C_6 ou un groupe alcoxy en C_1 à C_6, le groupe de formule OR^5 est un groupe hydroxy ou un groupe hydroxy protégé par un groupe alcanoyle en C_2 à C_7, et R^{32} et R^{42} sont chacun un groupe alcanoyle en C_2 à C_7, un groupe alcanoyle en C_2 à C_7 à substitution alcoxy en C_1 à C_6, un groupe alcanoyle en C_2 à C_7 à substitution amino, un groupe (alcoxy en C_1 à C_6)carbonyle ou un groupe phénoxycarbonyle.

20. Composé selon la revendication 19, dans lequel Ar est un groupe phényle à substitution alcoxy en C_1 à C_6, et R^{32} et R^{42} sont chacun un groupe alcanoyle en C_2 à C_7 à substitution alcoxy en C_1 à C_6.

21. Composition pharmaceutique qui comprend une quantité efficace, du point de vue thérapeutique, d'un composé tel qu'indiqué dans l'une quelconque des revendications 7 à 20 ou d'un sel acceptable en pharmacie de celui-ci, en mélange avec un véhicule ou diluant conventionnel acceptable en pharmacie.